



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 49/00, 49/04, 51/00, 31/13, 31/28,</b> <b>A01N 33/02</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 97/01360</b> <b>(43) International Publication Date:</b> 16 January 1997 (16.01.97)
<b>(21) International Application Number:</b> PCT/US96/10785 <b>(22) International Filing Date:</b> 24 June 1996 (24.06.96) <b>(30) Priority Data:</b> 60/000,524                      26 June 1995 (26.06.95)                      US 08/560,626                      20 November 1995 (20.11.95)                      US <b>(71) Applicant (for all designated States except US):</b> CONCAT, LTD. [US/US]; Suite 101, 3205 Northwood Drive, Concord, CA 94520 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> WINCHELL, Harry, S. [-/US]; 1 Via Oneg, Lafayette, CA 94549 (US). KLEIN, Joseph, Y. [-/IL]; 19 Naamat Street, 34670 Haifa (IL). SIMHON, Elliot, D. [-/IL]; 10 Klebanov Street, 32804 Haifa (IL). CYJON, Rosa, L. [-/IL]; 27 Burla Street, 32812 Haifa (IL). KLEIN, Ofer [-/IL]; 4 Mivtza Yehonatan Street, 34678 Haifa (IL). ZAKLAD, Haim [-/IL]; 22 Italia Street, 32812 Haifa (IL). <b>(74) Agents:</b> HEINES, M., Henry et al.; Townsend and Townsend and Crew L.L.P., Two Embarcadero Center, San Francisco, CA 94111-3834 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> COMPOUNDS WITH CHELATION AFFINITY AND SELECTIVITY FOR FIRST TRANSITION SERIES ELEMENTS, AND THEIR USE IN MEDICAL THERAPY AND DIAGNOSIS  <b>(57) Abstract</b> <p>This invention involves synthesis and use of a class of compounds with chelation affinity and selectivity for first transition series elements. Administration of the free or conjugated compound, or physiological salts of the free or conjugated compound, results in decrease in the <i>in vivo</i> bioavailability of first transition series elements and/or removal from the body of first transition series elements and elements with similar chemical properties. These characteristics make such compounds useful in the management of diseases associated with a bodily excess of first transition series elements and elements with similar chemical properties. This invention demonstrates that such compounds inhibit mammalian, bacterial, and fungal cell replication and are therefore useful in the treatment of neoplasia, infection, inflammation, immune response, and in termination of pregnancy. Since these compounds are capable of decreasing the <i>in vivo</i> availability of tissue iron they are useful in management of free radical mediated tissue damage, and oxidation mediated tissue damage. When combined with radioisotopic or paramagnetic cations of first transition series elements, or elements with chemical properties similar to those of first transition series elements, prior to their administration, the resulting complexes are useful as diagnostic agents in nuclear medicine and magnetic resonance imaging (MRI).</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<b>AM</b>	Armenia	<b>GB</b>	United Kingdom	<b>MW</b>	Malawi
<b>AT</b>	Austria	<b>GE</b>	Georgia	<b>MX</b>	Mexico
<b>AU</b>	Australia	<b>GN</b>	Guinea	<b>NE</b>	Niger
<b>BB</b>	Barbados	<b>GR</b>	Greece	<b>NL</b>	Netherlands
<b>BE</b>	Belgium	<b>HU</b>	Hungary	<b>NO</b>	Norway
<b>BF</b>	Burkina Faso	<b>IE</b>	Ireland	<b>NZ</b>	New Zealand
<b>BG</b>	Bulgaria	<b>IT</b>	Italy	<b>PL</b>	Poland
<b>BJ</b>	Benin	<b>JP</b>	Japan	<b>PT</b>	Portugal
<b>BR</b>	Brazil	<b>KE</b>	Kenya	<b>RO</b>	Romania
<b>BY</b>	Belarus	<b>KG</b>	Kyrgyzstan	<b>RU</b>	Russian Federation
<b>CA</b>	Canada	<b>KP</b>	Democratic People's Republic of Korea	<b>SD</b>	Sudan
<b>CF</b>	Central African Republic	<b>KR</b>	Republic of Korea	<b>SE</b>	Sweden
<b>CG</b>	Congo	<b>KZ</b>	Kazakhstan	<b>SG</b>	Singapore
<b>CH</b>	Switzerland	<b>LI</b>	Liechtenstein	<b>SI</b>	Slovenia
<b>CI</b>	Côte d'Ivoire	<b>LK</b>	Sri Lanka	<b>SK</b>	Slovakia
<b>CM</b>	Cameroon	<b>LR</b>	Liberia	<b>SN</b>	Senegal
<b>CN</b>	China	<b>LT</b>	Lithuania	<b>SZ</b>	Swaziland
<b>CS</b>	Czechoslovakia	<b>LU</b>	Luxembourg	<b>TD</b>	Chad
<b>CZ</b>	Czech Republic	<b>LV</b>	Latvia	<b>TG</b>	Togo
<b>DE</b>	Germany	<b>MC</b>	Monaco	<b>TJ</b>	Tajikistan
<b>DK</b>	Denmark	<b>MD</b>	Republic of Moldova	<b>TT</b>	Trinidad and Tobago
<b>EE</b>	Estonia	<b>MG</b>	Madagascar	<b>UA</b>	Ukraine
<b>ES</b>	Spain	<b>ML</b>	Mali	<b>UG</b>	Uganda
<b>FI</b>	Finland	<b>MN</b>	Mongolia	<b>US</b>	United States of America
<b>FR</b>	France	<b>MR</b>	Mauritania	<b>UZ</b>	Uzbekistan
<b>GA</b>	Gabon			<b>VN</b>	Viet Nam

COMPOUNDS WITH CHELATION AFFINITY AND SELECTIVITY FOR FIRST TRANSITION  
SERIES ELEMENTS, AND THEIR USE IN MEDICAL THERAPY AND DIAGNOSIS.

5

CROSS REFERENCE TO RELATED APPLICATION

This application is related to provisional application no.

10 60/000,524, filed June 26, 1995, and applications 08/543,425 and  
08/405,562, each of which is incorporated by reference herein for all legal  
purposes to be served thereby.

15 The present invention lies in the field of metal cation chelators  
(ligands) and their use for purposes of decreasing the bioavailability of elements  
of the first transition series, and/or the removal from the body of these  
elements or those with similar chemical properties. First transition series  
elements are components of enzymes required for nucleic acid replication as  
well as general cell replication. By inhibiting nucleic acid replication these  
agents are useful in inhibiting growth of DNA and RNA viruses. By inhibiting  
20 bacterial and fungal cell replication these agents are useful *in vitro* as  
preservatives, and employing topical or systemic *in vivo* administration they are  
useful in treating bacterial and fungal infections and in wound care. By  
inhibiting protozoan cell replication these agents are useful in treatment of  
protozoan infections. By inhibiting mammalian cell replication, these agents are  
25 useful in treating neoplastic disease, in suppression of the immune response, in  
inhibition of osteoclast activity, and in termination of pregnancy. Iron, a first  
transition element, is involved in free radical mediated tissue damage. By  
decreasing the body free iron content, these agents inhibit free radical mediated  
tissue damage. Excess of body iron characterizes hemochromatosis/-  
30 hemosiderosis, and excess of the first transition series element, copper,  
characterizes Wilson's disease. By removing either excess iron or copper from  
the body these agents are useful in treating these diseases. When combined

with elements possessing paramagnetic properties, the chelating agents described herein also find diagnostic utility as contrast enhancing agents in magnetic resonance imaging. When combined with radioactive elements, these chelating agents find utility in nuclear medical imaging.

5

## BACKGROUND OF THE INVENTION

Metal cations belonging to the first transition series are known to play important coenzymatic roles in metabolism. Zinc is known to be a coenzyme for over eighty different enzyme systems including those directly involved with DNA and RNA synthesis such as thymidine kinase, DNA and RNA polymerases, reverse transcriptase and terminal deoxynucleotide transferase. Among its other coenzyme functions, iron is the coenzyme for myoglobin, the cytochromes and catalases and is thus essential for oxidative metabolism. Manganese and copper also play significant coenzyme roles, and other metal cations in the first transition series are considered to be essential trace elements although their metabolic role is less well defined.

Compounds capable of forming complexes with metal cations, which compounds are commonly referred to as chelators or ligands, are known to have a variety of uses in medicine. These include their use as pharmaceuticals in treating heavy metal poisoning, in treating diseases associated with trace metal excess such as iron storage and copper storage diseases (hemosiderosis and Wilson's disease, respectively), as radiopharmaceutical agents in nuclear medical imaging when forming complexes with radioactive metals, as contrast enhancement agents in magnetic resonance imaging (MRI) when forming complexes with paramagnetic metals, and as contrast enhancement agents in radiography when forming complexes with heavy metals.

Examples of ligands employed in treating heavy metal poisoning such as that due to lead, mercury, and other metals, are ethylenediamine tetraacetic acid (EDTA) and diethylenetriamine pentaacetic acid (DTPA). The ligand desferrioxamine is used in treating iron storage disease, and the ligand

penicillamine is used in the mobilization of copper in the treatment of Wilson's disease.

Examples of complexes used to form radiopharmaceuticals useful in evaluations of the kidneys, bone and liver are complexes of technetium-99m ( $^{99m}\text{Tc}$ ) with diethylenetriamine pentaacetic acid (DTPA), dimercaptosuccinic acid (DMSA), methylene diphosphonate (MDP) and derivatives of iminodiacetic acid (IDA).

Complexes of paramagnetic metal cations which are useful as MRI contrast agents operate by accelerating proton relaxation rates. Most commonly a metal cation, such as gadolinium (III), having a large number of unpaired electrons is complexed by a ligand suitable for complexation of that cation. An example is gadolinium (III) complexed by DTPA.

Chelators with affinity for iron cations have been shown to inhibit cell proliferation. Desferrioxamine is one example of such a chelator. This effect is thought to be a consequence of the complexation of tissue iron by the chelator, which thereby deprives the proliferating cells of a source of iron for critical enzyme synthesis. Moreover, it is believed that certain types of tissue damage are mediated by the formation of free radicals. It is also appreciated that catalytically active iron catalyzes formation of the highly active hydroxyl free radical. Based on such relationships chelators (ligands) for iron such as desferrioxamine and the experimental iron chelator "L1" (1,2-dimethyl-3-hydroxypyrid-4-one) have been examined in management of conditions where free radical mediated tissue damage is believed to play a role, as well as in clinical management of conditions in which control of cell proliferation is desired. Conditions where the administration of iron chelators has been evaluated include: rheumatoid arthritis, anthracycline cardiac poisoning, reperfusion injury, solid tumors, hematologic cancers, malaria, renal failure, Alzheimer's disease, myelofibrosis, multiple sclerosis, drug-induced lung injury, graft versus host disease, and transplant rejection and preservation (Voest, E.E., *et al.*, "Iron Chelating Agents in Non-Iron Overload conditions," *Annals of Internal Medicine* 120(6): 490-499 (15 March 1994)).

Agents which inhibit cell replication have found use in the prior art as chemotherapeutic agents for treatment of neoplasia and infectious disease,

for suppression of the immune response, and for termination of pregnancy. Such agents usually act by inhibiting DNA, RNA or protein synthesis. This results in a greater adverse effect on rapidly proliferating cell populations than on cells "resting" in interphase or proliferating less rapidly.

5           Such agents may possess a degree of selectivity in treating the rapidly proliferating offending cell population, particularly in the case of certain neoplasias and infectious processes. These agents also inhibit replication of normal cells of the host organism, to varying degrees. Cells of the immune system proliferating in response to antigenic challenge are sensitive to such  
10 agents, and accordingly these agents are useful in suppressing the immunological response. Examples are the suppression of the homograft rejection response following tissue transplantation and the treatment of autoimmune disorders. Replication of protozoan, bacterial and mycotic microorganisms are also sensitive to such agents, which makes the agents  
15 useful in treating infections by such microorganisms.

          Agents which suppress cell replication by inhibiting DNA or RNA synthesis have primarily found utility in treatment of neoplastic diseases. The glutamine antagonists azaserine, DON, and the anti-purines such as  
20 6-mercaptopurine and 6-thioguanine principally inhibit DNA synthesis by their action on phosphoribosylpyrophosphate amidotransferase, the enzyme involved in the first step in purine nucleotide synthesis. The folic acid antagonists aminopterin and methotrexate inhibit DNA synthesis (and other synthetic processes involving one carbon transport) by inhibiting the dihydrofolate reductase enzyme system, thereby interfering with formation of  
25 tetrahydrofolate, which is necessary in transfer of one-carbon fragments to purine and pyrimidine rings. Hydroxyurea inhibits DNA synthesis by inhibiting ribonuclease reductase, thereby preventing reduction of ribonucleotides to their corresponding deoxyribonucleotides. The anti-pyrimidines such as  
30 5-fluorouracil inhibit DNA synthesis by inhibiting thymidylate synthetase. 5-Fluorouracil may also be incorporated into fraudulent RNA molecules. Bleomycin appears to inhibit DNA synthesis by blocking thymidine incorporation into DNA, although it may have other mechanisms of action. Agents such as 5-bromouracil and iododeoxyuridine may be incorporated into DNA in place of

thymidine, and cytosine arabinoside may be incorporated into DNA in place of 2'-deoxycytidine. The fraudulent DNA produced by these incorporations interferes with the information transmittal system for DNA→RNA→protein synthesis.

5 Alkylating agents used in treating neoplasias, such as the nitrogen mustards, ethylene imines, alkyl sulphonates and antibiotics such as mitomycin C, suppress cell replication by attacking DNA and forming covalent alkylate linkages within preformed DNA, thereby interfering with DNA function and replication. The activity of such agents is therefore not limited to inhibition of  
10 cell replication alone.

Agents used in treatment of neoplasias such as 8-azaguanidine and 5-fluorouracil inhibit cell replication by being incorporated into fraudulent RNA. Agents such as actinomycin D, daunorubicin, nogalomicin, mithramycin and adriamycin are thought to inhibit RNA polymerase by strongly binding to  
15 DNA and thereby inhibiting DNA to RNA transcription.

Certain agents which inhibit cell replication by arresting metaphase (examples of such agents are colchicine, vinblastine, vincristine, podophyllotoxin, and griseofulvin) or arresting telophase (cytochalasins) have also been shown to be active in treating neoplasias or microbial infections.

20 Agents which inhibit cell replication primarily by inhibition of protein synthesis have found utility in the treatment of microbial infections. The tetracyclines, streptomycins and neomycin, for example, inhibit protein synthesis by inhibition of the mRNA-ribosome-tRNA complex. Chloramphenicol, erythromycin, lincomycin, puromycin appear to inhibit protein  
25 synthesis by inhibition of the peptidyl synthetase reaction. A miscellaneous group of antibiotics appear to act by inhibition of translocation of the ribosome along mRNA. Penicillins act by inhibiting synthesis of the bacterial cell wall.

Complexes of heavy metals such as platinum have been found to be active in treatment of certain neoplasias. The inhibition of cell replication by  
30 these complexes is attributed to the *in vivo* hydrolysis of one or more of the coordinating ligand sites occupying positions in the coordination shell of the metal. This hydrolysis liberates the coordination sites for *in vivo* interaction with nucleophilic donor sites which are critical to replication or survival of the

cell population. There is a wide diversity of such donor sites *in vivo*, but it is believed that one critical set of donor sites involves binding of the platinum to two guanine or one guanine and one adenine residue of opposing strands of DNA.

5           The mechanisms of action of the various agents employed in treating protozoan infection are largely unknown. However, it has been demonstrated that agents which interfere with cell replication can be active in treating such infections. For example, the antimalarial agent chloroguanide and the diaminopyrimidines act as selective inhibitors of plasmodial dihydrofolate  
10           reductase thereby inhibiting plasmodial DNA replication. Tetracyclines possess antimalarial and antiprotozoal activities possibly acting by mechanisms similar to those operative in their inhibition of bacterial replication. The antibiotics puromycin and erythromycin, as well as tetracyclines which inhibit microbial replication, have also been employed in treatment of amebiasis. The  
15           antiprotozoal effects of the diamidines is believed to be due to their inhibition of cell replication by interference with DNA.

          Based on what is known from the action of the agents cited above, one can readily conclude that agents which inhibit cell replication, regardless of the specific biochemical mechanism involved, have utility in the  
20           treatment of a wide variety of neoplastic and infectious diseases and in the management of certain of the body's responses which are mediated through selective *in vivo* cell replication.

### SUMMARY OF THE INVENTION

25           The present invention resides in the discovery that a class of substituted polyaza compounds showing affinity and selectivity for first transition series elements (atomic numbers 21-30) are capable of inhibiting cell proliferation of mammalian, bacterial and yeast (fungal) cell populations and are therefore useful *in vitro* as preservatives and *in vivo*, administered topically or  
30           parenterally, in treatment of a wide variety of conditions including neoplasia, infection, inflammation, wound care, suppression of the immune response, inhibition of osteoclasts in treatment of osteoporosis and in termination of pregnancy. It is believed that the mechanism for inhibition of cell proliferation

by these compounds lies in their ability to decrease the bioavailability of essential first transition series elements. The term "decrease the bioavailability" is used herein to denote a reduction or elimination of the accessibility of these elements to biological systems and thereby a reduction or elimination of the ability of these elements to perform the functions they would otherwise perform in living systems. Since these compounds decrease the bioavailability of zinc and iron, they are useful in inhibiting replication of DNA and RNA viruses. Since these compounds decrease the *in vivo* availability of tissue iron, they are also useful in management of free radical-mediated tissue damage and oxidation-mediated tissue damage. The compounds can also be prepared as complexes with radioisotopic or paramagnetic cations of first transition series elements, or with elements having chemical properties similar to those of first transition series elements. Complexes prepared in this manner are useful as diagnostic agents in nuclear medicine and magnetic resonance imaging.

By virtue of their affinity and selectivity, these substituted polyaza compounds are effective in treating diseases characterized by excess of first transition series elements, such as hemosiderosis (iron) and Wilson's disease (copper).

For therapeutic purposes these agents may be employed in their free ligand form or in a protected form (for example, as the ester of the pendant donor group) where the protecting group can be removed *in vivo* by enzymatic action to release the active ligand form. The agents can be administered as either the free chelator, as a protected form of the chelator, or as physiological salts of these forms. Physiologically and pharmacologically acceptable salts of these compounds dissolved in suitable vehicles are fully suitable for use as pharmaceutical agents.

These compounds of this invention are chemically distinct from previously known antibiotic and chemotherapeutic agents which affect cell proliferation and which might also possess some properties as metal ion ligands. Unlike the chemotherapeutic complexes between a ligand and a heavy metal cation (such as platinum, for example) in which the complexed heavy metal provides the basis for the therapeutic effect and the purpose of the

ligand portion of the complex is related to the *in vivo* distribution and hydrolysis rates of the complex, the compounds of this invention are active in the form of the metal-free ligand and do not require the addition of a heavy metal to exercise their therapeutic effect. The compounds of the invention are also chemically distinct from agents previously employed clinically as chelators of certain first transition series elements (such as desferrioxamine and 1,2-dimethyl-3-hydroxypyrid-4-one for chelation of iron, and penicillamine for chelation of copper).

Subclasses of compounds of this invention are novel compounds, structurally distinct from previously disclosed chelators and any complexes derived therefrom. Complexes of these subclasses in combination with radioisotopes or paramagnetic cations are particularly useful in diagnostic studies in nuclear medicine or in magnetic resonance imaging, respectively.

## DETAILED DESCRIPTION OF THE INVENTION

### Abbreviations

Abbreviations are used herein, in conformance with standard chemical practice, as follows: Bz, benzyl; Me, methyl; Et, ethyl; Pr, propyl; <sup>i</sup>Pr, isopropyl; <sup>i</sup>Bu, isobutyl; Bu, butyl; <sup>t</sup>Bu, *tertiary*-butyl; Ts, *para*-toluenesulfonyl; Tf<sup>-</sup>, trifluoroacetate; DMSO, dimethylsulfoxide; DMF, dimethylformamide; DEK, diethyl ketone (3-pentanone); MeOH, methanol; LDA, lithium diisopropylamide; THF, tetrahydrofuran; Py, pyridine; Ac, acetyl; Ac<sub>2</sub>O, acetic anhydride

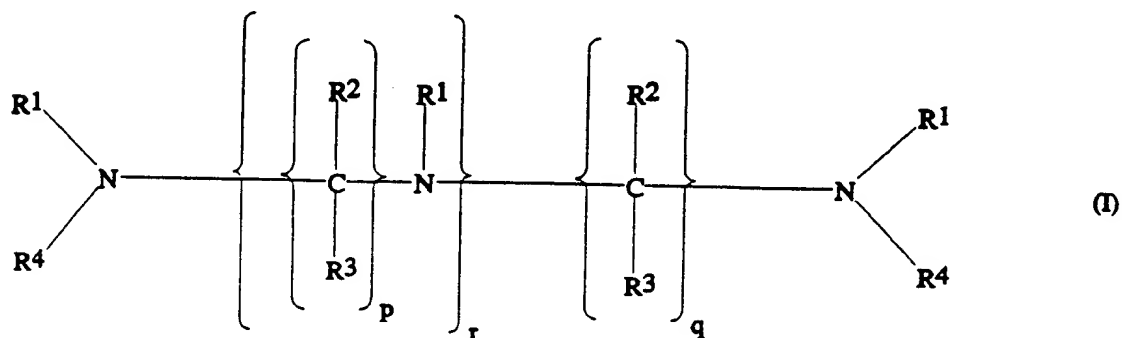
### Embodiments of the Invention

The present invention provides methods of *in vitro* and *in vivo* complexing of first transition series element cations. The invention further provides methods of treating conditions dependent on the bioavailability of first transition series elements and also conditions associated with elevated levels of first transition series elements. Diagnostic methods are also provided which are useful in nuclear medicine and magnetic resonance imaging. The *in vivo* methods involve administering to a patient or host, a chelating agent (or ligand) which is capable of complexing first transition series elements as well as

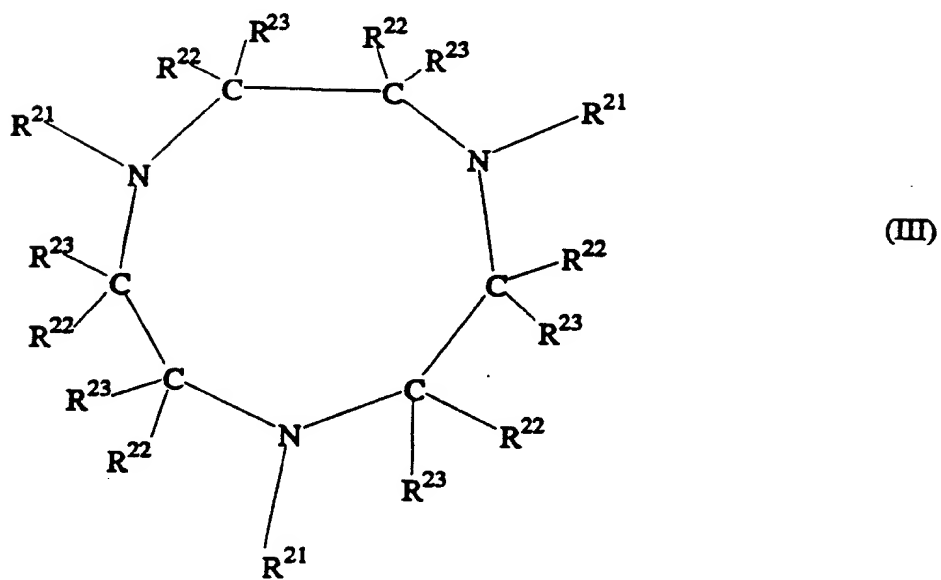
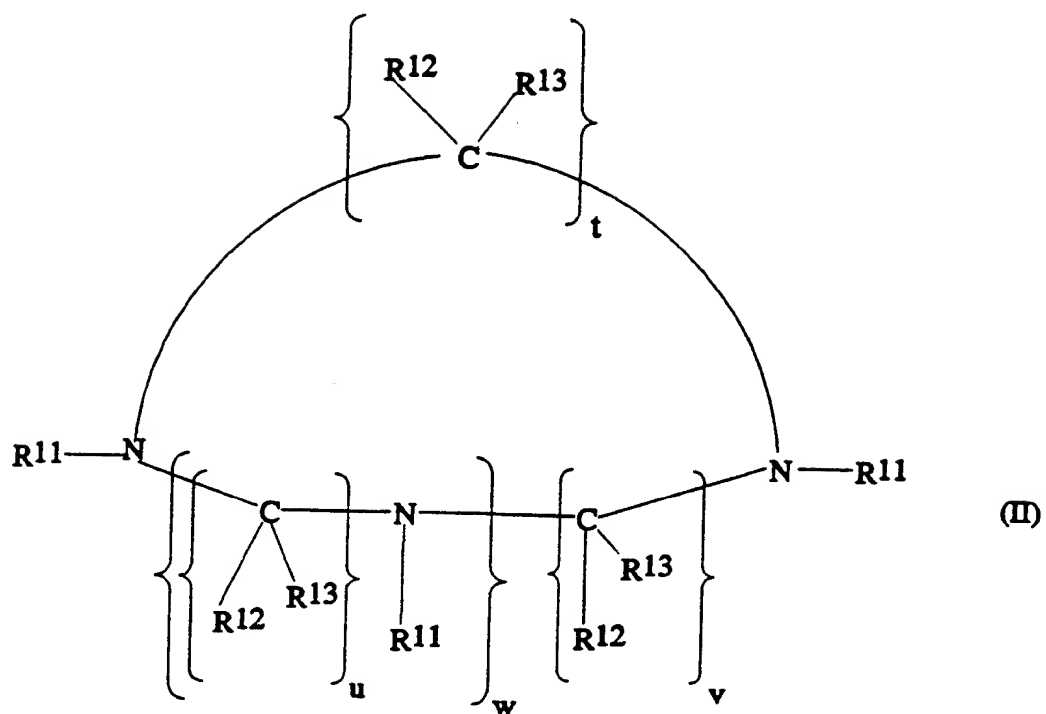
elements with chemical characteristics similar to those of first transition series elements. For the diagnostic methods, the chelating agent is administered as a complex of radioisotopic or paramagnetic cations of first transition series elements (or those with similar properties).

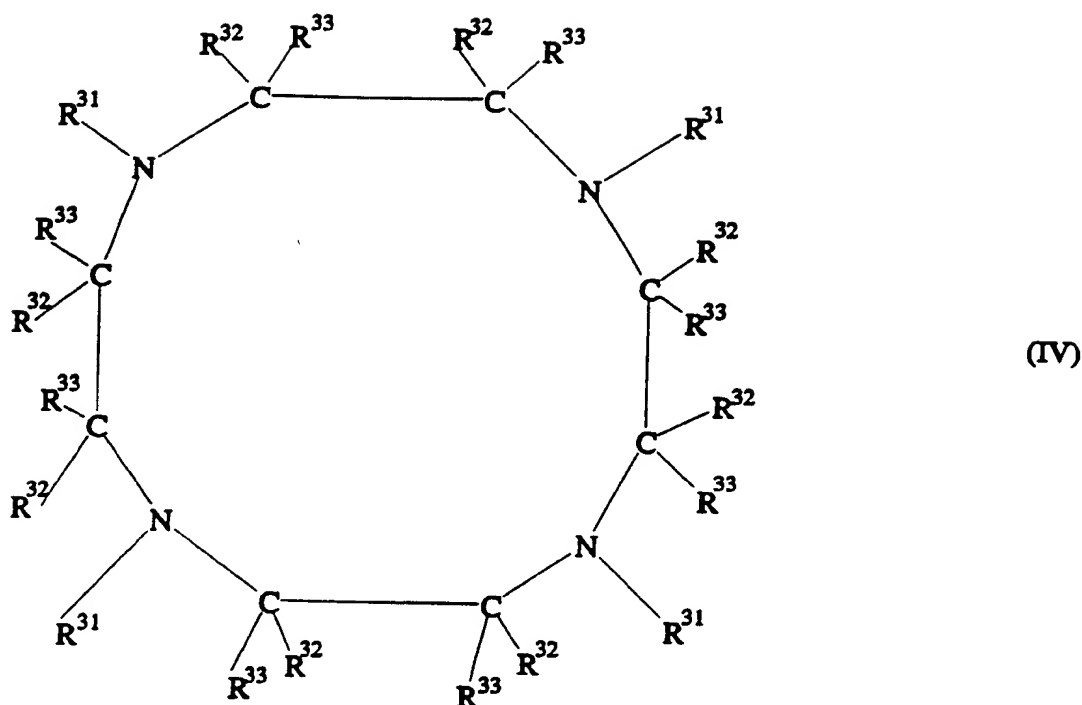
5

Among the ligands used in the practice of the present invention are the embodiments represented by the following formulas:



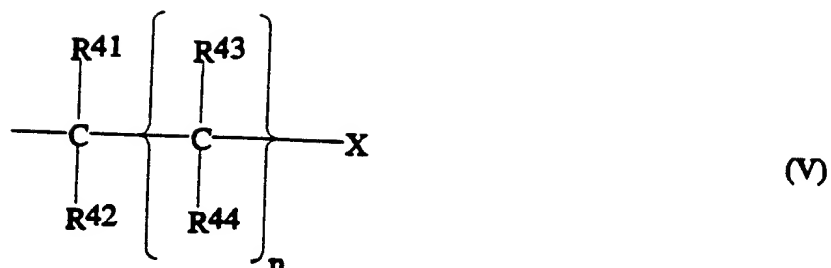
10





In Formulas I through IV,  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  may be the same or different on any single molecule, and the same is true for  $R^{11}$ ,  $R^{12}$ , and  $R^{13}$ , for  $R^{21}$ ,  $R^{22}$ , and  $R^{23}$ , and for  $R^{31}$ ,  $R^{32}$ , and  $R^{33}$ . Each of these symbols ( $R^1$  through  $R^{33}$ ) represents H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa (-O-), alkenyl interrupted by one or more oxa (-O-), alkyl interrupted by thia (-S-), alkenyl interrupted by thia (-S-), aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, or hydroxyarylalkyl, provided only that these groups do not interfere with complexation and they are not combined in a manner which results in a chemically unstable configuration. The alkyl, alkenyl and aryl groups, or portions of groups, in the foregoing list can also be substituted with one or more halogen atoms.

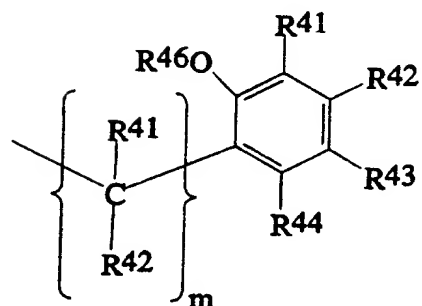
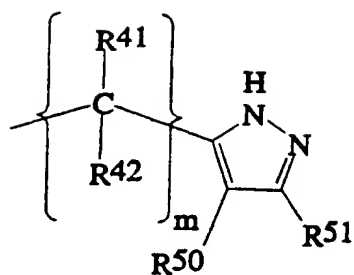
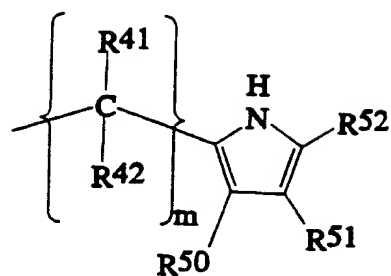
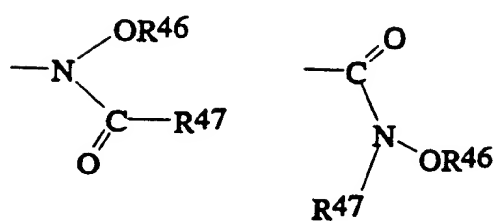
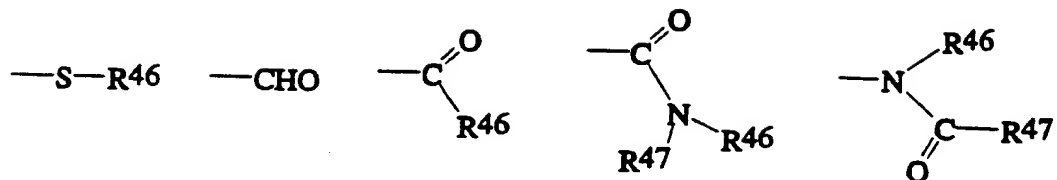
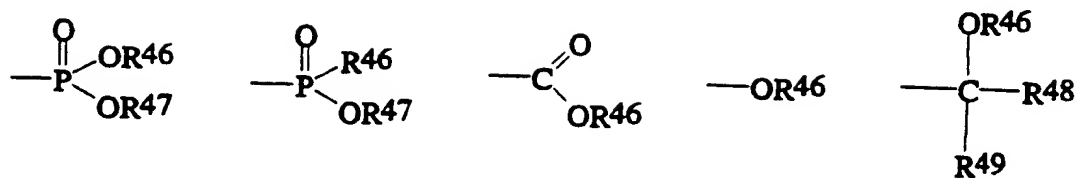
In addition to the radicals and radical subclasses listed above,  $R^1$ ,  $R^4$ ,  $R^{11}$ ,  $R^{21}$  and  $R^{31}$  are further defined to include:

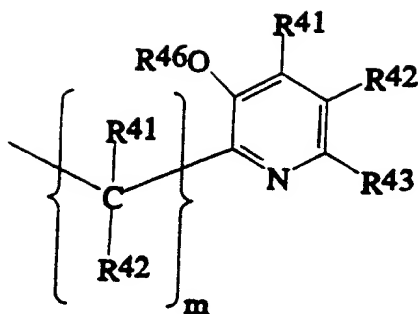


In Formula V,  $\text{R}^{41}$ ,  $\text{R}^{42}$ , and  $\text{R}^{43}$  may be the same or different on any single radical, and are defined as H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa (-O-), alkenyl interrupted by oxa (-O-), alkyl interrupted by thia (-S-), alkenyl interrupted by thia (-S-), aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, or hydroxyarylalkyl, provided only that these groups do not interfere with complexation and that they are not combined in a manner which results in a chemically unstable configuration. Here as well, the alkyl, alkenyl and aryl groups, or portions of groups, in the list can be substituted with one or more halogen atoms.  $\text{R}^{44}$  in Formula V is defined as H, hydroxy, amino, alkyl, alkyl interrupted by oxa (-O-), alkoxy, aryl, aryloxyalkyl, alkoxyaryl, or any of these groups in which the alkyl and aryl portions are substituted with one or more halogen atoms. Again, the groups are selected such that they do not interfere with complexation and are not combined in a manner which results in a chemically unstable configuration.

The index  $n$  is either zero or 1.

The symbol X represents any of the following groups:





In these formulas, R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup>, and R<sup>44</sup> may be the same or different on any single radical, and have the same definitions as R<sup>41</sup>, R<sup>42</sup>, and R<sup>43</sup> given above.

R<sup>46</sup>, R<sup>47</sup>, R<sup>48</sup> and R<sup>49</sup> may be the same or different on any single radical, and are each defined as H, or alkyl or aryl groups which do not interfere with complexation. R<sup>46</sup> and R<sup>47</sup> may further be combined as a single divalent group, thereby forming a ring structure. R<sup>48</sup> and R<sup>49</sup> are further defined to include alkoxy, alkyl interrupted by oxa (-O-), aryloxyalkyl, and alkoxyaryl, combined in a manner which results in a chemically stable configuration. All alkyl and aryl groups in this paragraph, including alkyl and aryl portions of groups, are optionally substituted with one or more halogen atoms.

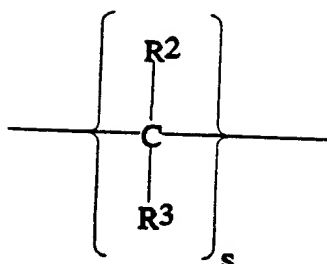
R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> may be the same or different on any single radical, and are each defined as H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, or hydroxyarylalkyl.

The index m is an integer which is either 1, 2 or 3.

Returning to Formulas I through IV, further variations within the scope of this invention are as follows:

(1) Internal cyclizations within these formulas at the nitrogen atoms, formed by joining together any two of the R<sup>1</sup> and R<sup>2</sup> groups in Formula I, any two of the R<sup>11</sup> groups in Formula II, any two of the R<sup>21</sup> groups in Formula III, or any two of the R<sup>31</sup> groups in Formula IV, as a single divalent group bridging the two nitrogen atoms, the single divalent group having the formula

15



(VI)

in which  $\text{R}^2$  and  $\text{R}^3$  are as defined above, and  $s$  is at least 2, preferably 2 or 3;

5

(2) Dimers or other two-molecule combinations of Formulas I through IV (the molecules being the same or different), formed by bridging the molecules together through one or more divalent groups of Formula VI (as defined above) substituted for any one or two of the  $\text{R}^{11}$  groups in Formula II, any one or two of the  $\text{R}^{21}$  groups in Formula III, or any one or two of the  $\text{R}^{31}$  groups in Formula IV;

10

(3) Internal cyclizations at common carbon atoms within these formulas to form homocyclic rings, by joining one or more of the  $\text{R}^2$ ,  $\text{R}^{12}$ ,  $\text{R}^{22}$ , or  $\text{R}^{32}$  groups to one or more of the  $\text{R}^3$ ,  $\text{R}^{13}$ ,  $\text{R}^{23}$ , or  $\text{R}^{33}$  groups at the same carbon atom, as a single divalent group of Formula VI (as defined above), and forming one or more such homocyclic rings per structure in this manner; and

15

(4) Internal cyclizations involving two carbon atoms separated by a nitrogen atom within these formulas to form heterocyclic rings, by joining any two adjacent  $\text{R}^2$  groups in Formula I, any two adjacent  $\text{R}^{12}$  groups in Formula II, any two adjacent  $\text{R}^{22}$  groups in Formula III, or any two adjacent  $\text{R}^{32}$  groups in Formula IV, as a single divalent group of Formula VI (as defined above), and forming one or more such heterocyclic rings per structure in this manner.

20

In Formula I, the subscripts  $p$  and  $q$  may be the same or different, and are each either 2 or 3. The subscript  $r$  is 0 to 4 inclusive, preferably 1 to 2 inclusive.

25

In Formula II,  $t$ ,  $u$  and  $v$  may be the same or different, and are each either 2 or 3. The value of  $w$  is at least 1, more preferably 1 to 4

inclusive, still more preferably 1 to 3 inclusive, and most preferably either 1 or 2.

5 The terms used in connection with these formulas have the same meaning here as they have in the chemical industry among those skilled in the art. The term "alkyl" thus encompasses both straight-chain and branched-chain groups and includes both linear and cyclic groups. The term "alkenyl" refers to unsaturated groups with one or more double bonds and includes both linear and cyclic groups. The term "aryl" refers to aromatic groups of one or more cycles.

10 For all such groups, those which are useful in the present invention are those which do not impair or interfere with the formation of chelate complexes. Within this limitation, however, the groups may vary widely in size and configuration. Preferred alkyl groups are those having 1 to 8 carbon atoms, with 1 to 4 carbon atoms more preferred. Prime examples are methyl, ethyl, isopropyl, *n*-butyl and *tert*-butyl. Preferred aryl groups are phenyl and naphthyl, particularly phenyl. Preferred aryl alkyl groups are phenylethyl and benzyl, and of these benzyl is the most preferred. Preferred cycloalkyl groups are those with 4 to 7 carbon atoms in the cycle, with cycles of 5 or 6 carbon atoms particularly preferred. Preferred halogen atoms are chlorine and fluorine, with fluorine particularly preferred.

20 One particularly preferred subclass of compounds within Formula I are those in which  $R^1$  is alkyl, alkenyl, aryl, arylalkyl, or cycloalkyl, substituted at the  $\beta$ -position with hydroxy. Likewise,  $R^{11}$  in Formula II,  $R^{21}$  in Formula III, and  $R^{31}$  in Formula IV are each preferably alkyl, alkenyl, aryl, arylalkyl, or cycloalkyl, substituted at the  $\beta$ -position with hydroxy. Further preferred are compounds in which one or more, and preferably two or more, of such groups ( $R^1$ ,  $R^{11}$ ,  $R^{21}$  and  $R^{31}$  on the same formula are substituted at the  $\beta$ -position with hydroxy. Still further preferred are compounds in which the  $\beta$ -hydroxy substituted groups are further substituted at the  $\beta$ -position with at least one hydroxymethyl, alkoxymethyl, alkenoxymethyl, aryloxymethyl, or combinations thereof, all of which may also be further substituted with halogen. Included among these are compounds of Formula III in which one or more of the  $R^{21}$  groups are substituted at the  $\beta$ -position with hydroxy and also with hydroxymethyl, alkoxymethyl, alkenoxymethyl, or aryloxymethyl, all of

which may also be further substituted with halogen, and the  $R^{22}$  and  $R^{23}$  groups are all hydrogen atoms.

Certain specific groups for  $R^1$ ,  $R^{11}$ ,  $R^{21}$ , and  $R^{31}$  are particularly preferred. These are: 2-hydroxy(2,2-diisopropoxymethyl)ethyl and  
5 (3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl.

For use in the present inventive methods, the complexes will preferably have a molecular weight which does not exceed 2000. More preferably the complexes will have molecular weights of from 200 to 1800, still more preferably of from 400 to 1100.

10 Among the complexes used in the practice of the present invention are the embodiments represented by the complexes formed between the ligands described above and paramagnetic metal cations or radioisotopic metal cations. These paramagnetic metal cations include elements of atomic numbers 22 through 29 (inclusive), 42, 44 and 58 through 70 (inclusive). Of  
15 these, the ones having atomic numbers 22 through 29 (inclusive) and 58 through 70 (inclusive) are preferred, and those having atomic numbers 24 through 29 (inclusive) and 64 through 68 (inclusive) are most preferred. Examples of such metals are chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium  
20 (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III). Chromium (III), manganese (II), iron (III) and gadolinium (III) are particularly preferred, with gadolinium (III) the most preferred.

Some methods of the present invention will use radioisotopic labels which will facilitate imaging of various disease states including tumors,  
25 inflamed joints or lesions or suspected lesions. The use of gamma emitting radioisotopes is particularly advantageous as they can easily be counted in a scintillation well counter, do not require tissue homogenization prior to counting, and can be imaged with gamma cameras.

Gamma or positron emitting radioisotopes are typically used in  
30 accordance with well known techniques. Suitable gamma-emitting radioisotopes include  $^{99}\text{Tc}$ ,  $^{51}\text{Cr}$ ,  $^{59}\text{Fe}$ ,  $^{67}\text{Ga}$ ,  $^{86}\text{Rb}$ ,  $^{111}\text{In}$  and  $^{195}\text{Pt}$ . Suitable positron-emitters include  $^{68}\text{Ga}$ .

Where indicated, physiologically or pharmacologically compatible salts of the ligands, or complexes thereof, which have an excess of acidic groups are formed by neutralizing the acidic moieties of the ligand with physiologically or pharmacologically compatible cations from corresponding inorganic and organic bases and amino acids. Examples are alkali and alkaline earth metal cations, notably sodium. Further examples are primary, secondary and tertiary amines, notably, ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, and N-methylglucamine (commonly referred to as "meglumine"). Examples of amino acid cations are lysines, arginines and ornithines.

Similarly, physiologically and pharmacologically compatible salts of those ligands which have an excess of basic groups are formed by neutralizing the basic moieties of the ligand with physiologically or pharmacologically compatible anions from corresponding inorganic and organic acids. Examples are halide anions, notably chloride. Further examples are sulfates, bicarbonate, acetate, pyruvate and other inorganic and organic acids.

Pharmaceutical compositions comprising the chelates described herein are prepared and administered according to standard techniques. The pharmaceutical compositions can be administered parenterally, *i.e.*, intraarticularly, intravenously, subcutaneously, or intramuscularly. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed. (1985).

The chelate compositions can be administered intravenously. Thus, this invention provides compositions for intravenous administration which comprise a solution of the chelate suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, *e.g.*, water, buffered water, 0.9% isotonic saline, and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate

physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, *etc.*

5           The concentration of chelates, in the pharmaceutical formulations can vary widely, *i.e.*, from less than about 0.05%, usually at or at least about 2-5% to as much as 10 to 30% by weight and will be selected primarily by fluid volumes, viscosities, *etc.*, in accordance with the particular mode of administration selected. For diagnosis, the amount of chelates in administered  
10 complexes will depend upon the particular metal cation being used and the judgement of the clinician. For use in magnetic resonance imaging the dose typically is between 0.05 to 0.5 millimoles/kg body weight.

          In general, any conventional method for visualizing diagnostic imaging can be used, depending upon the label used. Usually gamma and  
15 positron emitting radioisotopes are used for imaging in nuclear medicine and paramagnetic metal cations are used in magnetic resonance imaging.

          The methods of the present invention may be practiced in a variety of hosts. Preferred hosts include mammalian species, such as humans, non-human primates, dogs, cats, cattle, horses, sheep, and the like.

20           The foregoing description and the following examples are offered primarily for illustration and not as limitations. It will be readily apparent to those of ordinary skill in the art that the operating conditions, materials, procedural steps and other parameters of the compositions and methods described herein may be further modified or substituted in various ways  
25 without departing from the spirit and scope of the invention.

## EXAMPLES

### EXAMPLE 1

30           This example illustrates the synthesis of chelators (ligands) which are useful in the present invention. Section 1.1 illustrates the synthesis of

polyaza bases. Section 1.2 illustrates the synthesis of alkylating groups. Section 1.3 illustrates the preparation of chelating agents from alkylation of polyaza bases.

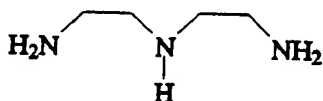
In all examples reactions were carried out in common solvents, compounds were purified by routine methodology and identity was established by proton NMR. In some cases identity was further verified by elemental analysis, mass spectroscopy, C-13 or P-31 NMR, or by synthesis of the identical compound by an independent alternate synthesis route.

### 1.1 SYNTHESIS OF POLYAZA BASES

Ethylene diamine (1.1.0), diethylene triamine (1.1.1), triethylenetetramine (1.1.2), 1,4,7-triazacyclononane (1.1.3), 1,4,7,10-tetraazacyclododecane (1.1.4), 1,4,8,11-tetraazacyclotetradecane (1.1.5) & 1,5,9,13-tetraazacyclohexadecane (1.1.6) and the corresponding hydrohalide salts were either obtained from commercial sources or were synthesized employing established methods and were used directly in the syntheses of chelators (ligands) described in section 1.3. Additional polyaza bases were synthesized as described herein.



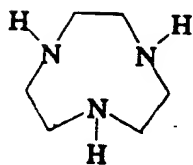
1.1.0



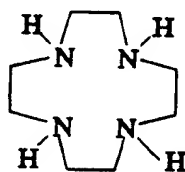
1.1.1



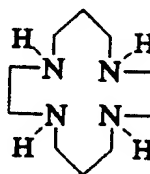
1.1.2



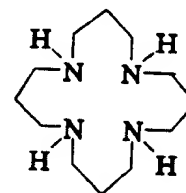
1.1.3



1.1.4



1.1.5

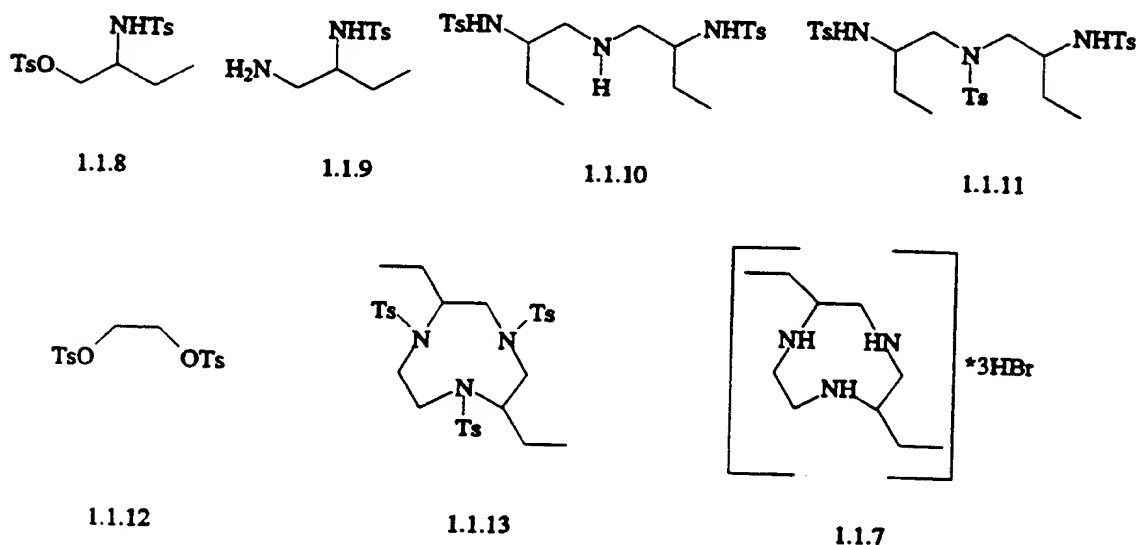


1.1.6

1.1.7 2,6-Diethyl-1,4,7-triazacyclononane trihydrobromide  
2-(p-toluenesulfonylamino)-1-(p-toluenesulfonyloxy) butane (1.1.8)  
and ammonium hydroxide were reacted to form 2-(p-toluenesulfonamino)-1-

## 21

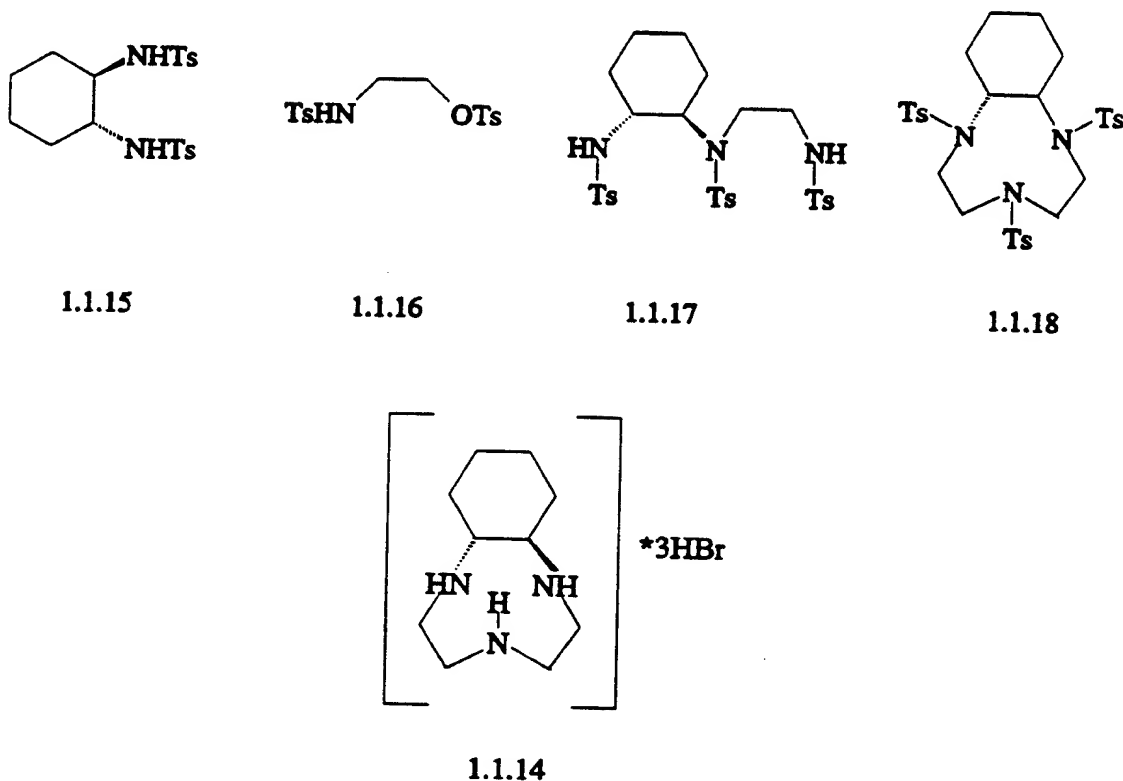
aminobutane (1.1.9). This was reacted with 2-(p-toluenesulfonylamino)-1-(p-toluenesulfonyloxy)butane (1.1.8) and potassium carbonate. The 3,7 bis(p-toluenesulfonylamino)-5-azanonane (1.1.10) product was purified by chromatography and reacted with p-toluenesulfonyl chloride to obtain the corresponding tri-p-toluenesulfonyl compound 3,7 bis(p-toluenesulfonylamino)-5-(p-toluenesulfonyl)-5-azanonane (1.1.11). This was purified by chromatography and reacted with 2.2 equivalents of sodium amide in DMF and then with 1,2-di(p-toluenesulfonyloxy)ethane (1.1.12). The 2,6-diethyl-1,4,7-tris(p-toluenesulfonyl) triazacyclononane (1.1.13) that was obtained following purification was heated in a solution of HBr in acetic acid to remove the p-toluenesulfonyl groups and form the titled compound (1.1.7)



1.1.14      1,4,7-Triazabicyclo[7.4.0<sup>8,13</sup>]tridecane trihydrobromide

1,2-trans-bis(p-toluenesulfonylamino)cyclohexane (1.1.15) was treated with NaH in DMSO. 1-(p-toluenesulfonylamino)-2-(p-toluenesulfonyl) ethane (1.1.16) was added to obtain 1-(p-toluenesulfonylamino)-2-[N-p-toluenesulfonyl-N-(2-p-toluenesulfonylaminoethyl)] aminocyclohexane (1.1.17). This was separated and reacted with NaH and 1,2-di(p-toluenesulfonyloxy)ethane (1.1.12) was added. The 2,3-butano-N,N'N"-tris(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.1.18) obtained was purified by chromatography. The p-toluenesulfonyl groups were removed by reaction in

HBr/Acetic acid and the 2,3-butano-1,4,7-triazacyclononane trihydrobromide (1.1.14) product precipitated from solution as the hydrobromide salt.



5

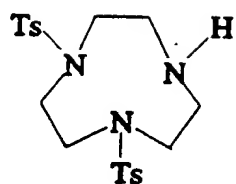
### 1.1.19      1,3-Bis (1,4,7-triazacyclononane) propane

N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.1.20) was prepared by reacting (1.1.3) with two equivalents of p-toluenesulfonyl chloride. Two equivalents of N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.1.20) hydrobromide were reacted with one equivalent of 1,3-diiodopropane in acetonitrile with excess potassium carbonate. 1,3-Bis[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane]propane (1.1.21) was isolated and purified by chromatography. The p-toluenesulfonyl groups were removed using sulfuric acid and HBr to yield the title compound (1.1.19).

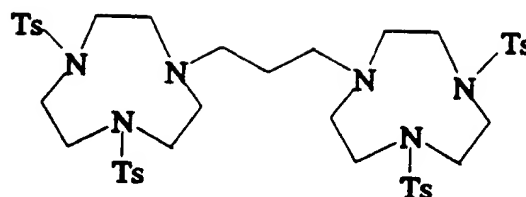
10

15

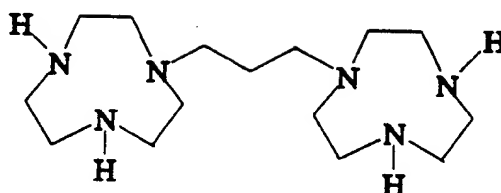
23



1.1.20



1.1.21



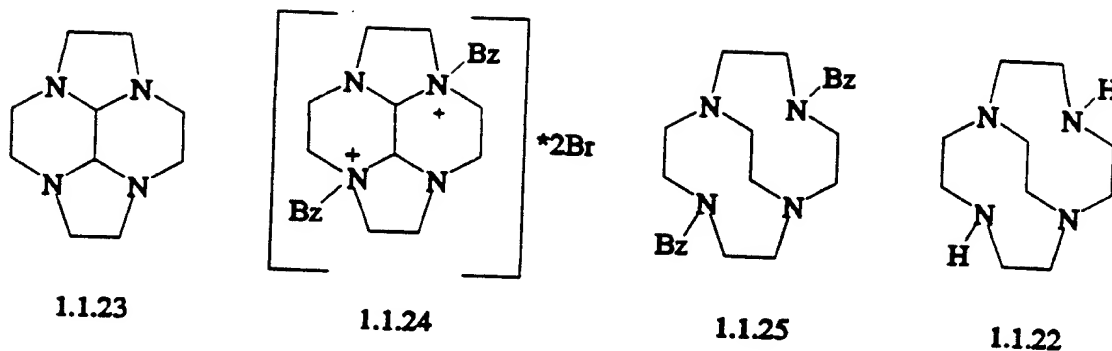
1.1.19

**1.1.22 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane**

5 1,4,7,10-tetraazadodecane (1.1.4) trihydrobromide in acetonitrile with potassium carbonate was reacted with glyoxal to form 1,4,7,10-tetraazatetracyclo-[5,5,2,0<sup>4,13</sup>,0<sup>10,14</sup>] tetradecane (1.1.23). Following separation the pure product was obtained by low pressure distillation. This was dissolved in acetonitrile and benzylbromide was added to form 1,7-dibenzylonium-1,4,7,10-tetraazatetracyclo[5,5,2,0<sup>4,13</sup>,0<sup>10,14</sup>] tetradecane

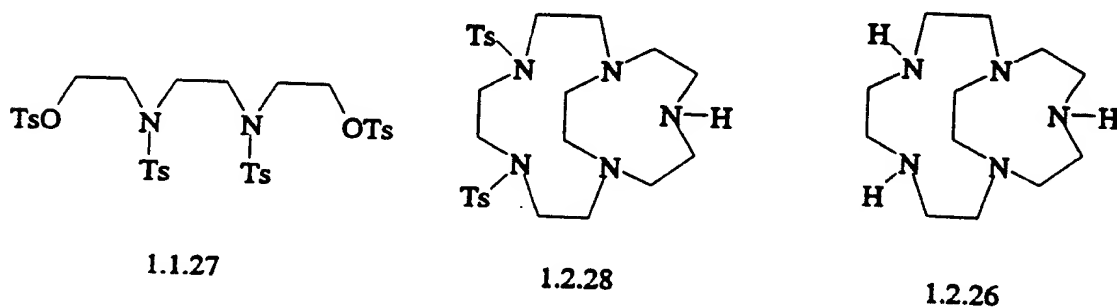
10 (1.1.24). Following recrystallization from ethanol this was reacted with sodium borohydride. HCl was added, followed by water and NaOH, and the product extracted with chloroform. Following evaporation of solvent the solids were dissolved in methanol and HBr was added to obtain 1,7-dibenzyl-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane (1.1.25) as the hydrobromide salt. This

15 was dissolved in water and reduced using H<sub>2</sub> and a Pd-C catalyst to remove the benzyl groups. Purification of the title compound was by crystallization of the hydrobromide salt. The base form was obtained by low pressure distillation following addition of base.



**1.1.26      1,4,7,10,13-Pentaazabicyclo [8.5.2] heptadecane.**

5      To 1,8-bis(p-toluenesulfonyloxy)-3,6-bis(p-toluenesulfonyl)-3,6-diazaoctane(1.1.27) was added 1,4,7-triazacyclononane(1.1.3) in acetonitrile with potassium bicarbonate to obtain 4,7-bis (p-toluenesulfonyl)-1,4,7,10,13-pentaazabicyclo [8.5.2] (1.1.28) heptadecane. The title compound was purified and the p-toluenesulfonyl groups were removed by treatment in sulfuric acid. Purification was done by low pressure distillation.

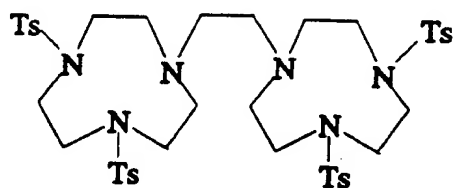


**1.1.29      1,2-Bis(1,4,7-triazabicyclononane-1-yl) ethane.**

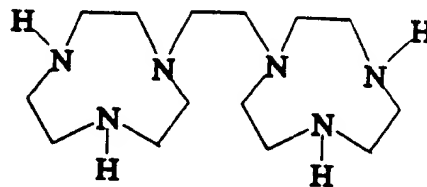
10      A mixture of N,N'-bis(p-toluenesulfonyl)-1,4,7-triazabicyclonone hydrobromide (1.1.13.33), ethylene glycol di-p-toluenesulfonyl or  
15      dibromoethane and excess of potassium carbonate in acetonitrile was refluxed overnight. The reaction mixture was added to water and extracted with methylene chloride. The tetratosylated product (1.1.30) was purified by chromatography. It was suspended in 70% H<sub>2</sub>SO<sub>4</sub> and heated at 150°C for 15  
20      hrs. The reactions cooled to room temperature and then 62% HBr solution was added. The white precipitate was collected and washed with ethanol. It was

25

redissolved in water and filtered from tars. The water was made basic and the title compound (1.1.29) was extracted with chloroform.



1.1.30



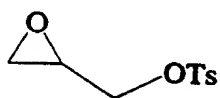
1.1.29

## 5 1.2 SYNTHESIS OF ALKYLATING GROUPS FOR ALKYLATION OF POLYAZA BASES TO FORM CHELATORS DESCRIBED IN EXAMPLE 1.3.

### 1.2.1 Preparation of Glycidyl Ethers

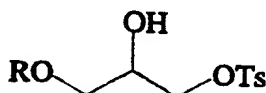
10 Glycidyl tosylate (R, S or d,l) (1.2.1.0) was reacted in the appropriate alcohol solvent employing catalytic amounts of conc.  $H_2SO_4$  or equivalent amounts of tetrafluoroboranetherate. The 1-alkyloxy-2-hydroxy-3-p-toluenesulfonyloxypropane (1.2.1.1) product was reacted in ether with BuLi to yield the title epoxide. The following compounds were prepared in this manner.

15 1.2.1.0 Glycidyl tosylate (R,S or d,l; commercially available).



1.2.1.0

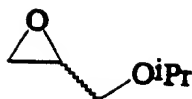
1.2.1.1 1-Alkyloxy-2-hydroxy-3-p-toluenesulfonyloxypropane.



1.2.1.1

20 1.2.1.2 d,l-Glycidyl-isopropyl ether (commercially available).

26

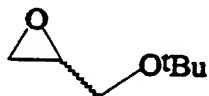


1.2.1.2

1.2.1.3 (2R) Glycidyl-isopropyl ether.

5 1.2.1.4 (2S) Glycidyl-isopropyl ether.

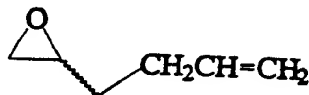
1.2.1.5 d,l-Glycidyl-t-butyl ether.



1.2.1.5

10 1.2.1.6 (2R) Glycidyl-t-butyl ether.

1.2.1.7 d,l-Glycidyl allyl ether.



1.2.1.7

15 1.2.1.8 d,l-Glycidyl phenyl ether

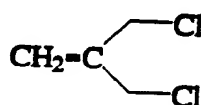


1.2.1.8

1.2.2 Preparation of 2,2-Dialkoxymethylene Oxiranes and Spiro-Oxiranes

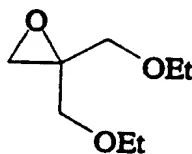
3-Chloro-2-chloromethyl-1-propane (1.2.2.0) was reacted with the corresponding sodium alkylate or disodium dialkylate either using the same alcohol or dialcohol as solvent or using an inert solvent. The ether product was purified by distillation or chromatography. Epoxidation was performed using *meta*-chloroperbenzoic acid in halogenated solvent. The following compounds were prepared in this manner.

1.2.2.0 3-Chloro-2-chloromethyl-1-propane (commercially available).



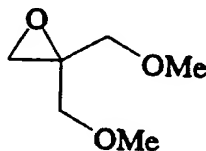
1.2.2.0

1.2.2.1. 2,2-Bis-ethoxymethyl oxirane.



1.2.2.1

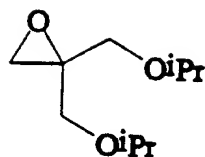
1.2.2.2 2,2-Bis-methoxymethyl oxirane.



1.2.2.2

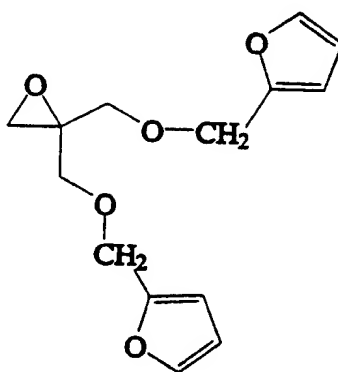
1.2.2.3 2,2-Bis-isopropyloxymethyl oxirane.

28



1.2.2.3

#### 1.2.2.4 2,2-Bis-difurfuryloxymethyl oxirane.

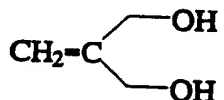


1.2.2.4

5

#### 1.2.2.5 2, 2-Bis(hydroxymethyl) oxirane

From 2-methylidene-1, 3-dihydroxypropanediol (commercially available).



1.2.2.5

10

#### 1.2.3 Preparation of Oxiranespiro-3-(1,5-Dioxacycloalkanes).

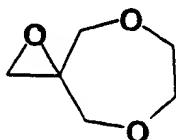
Various dry glycols in DMF were reacted with NaH and 3-chloromethyl-1-propane (1.2.2.0) was added to the resulting reaction mixture. Following completion of the reaction the solvents were removed and the product purified by low pressure distillation. The purified product in

15

29

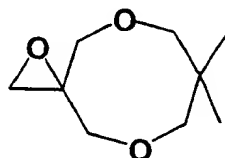
dichloroethane was reacted with m-chloroperbenzoic acid to form the corresponding epoxide. Following workup, the epoxide product was purified by distillation. The following compounds were prepared in this manner.

- 5      1.2.3.1      Oxiranespiro-3-(1,5-dioxacycloheptane).  
(From ethylene glycol)



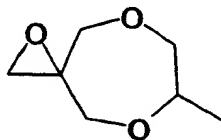
1.2.3.1

- 10      1.2.3.2      Oxiranespiro-3-(1,5-dioxo-7,7-dimethylcyclooctane).  
(From 2,2-dimethyl propylene glycol)



1.2.3.2

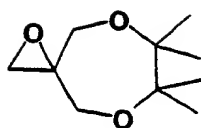
- 1.2.3.3      Oxiranespiro-3-(1,5-dioxo-6-methylcycloheptane).  
(From 1, 2- dihydroxy propane)



1.2.3.3

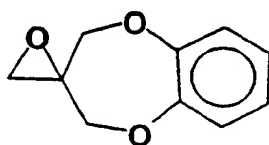
- 15      1.2.3.4      Oxiranespiro-3-(1,5-dioxo-6,6,7,7-tetramethylcycloheptane).  
[From 2,3-dihydroxy-2,3-dimethyl butane (pinacol)].

30



1.2.3.4

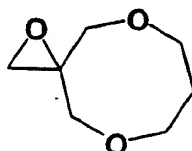
- 1.2.3.5 Oxiranespiro-3-(benzo[b]-1,5-dioxacycloheptane).  
(From 1,2-dihydroxybenzene).



1.2.3.5

5

- 1.2.3.6 Oxiranespiro-3-(1,5-dioxacyclooctane).  
(From 1,3-propanediol)



1.2.3.6

10

- 1.2.4 Preparation of Miscellaneous Epoxides

- 1.2.4.1 2,2-dimethyl oxirane.  
(From 2-methyl-1-propene and m-chloroperbenzoic acid.

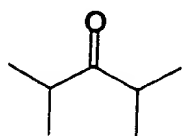


1.2.4.1

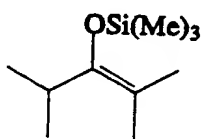
15

**1.2.4.2 2-(Isopropyl)-2-[(1-fluoro-1-methyl)ethyl] oxirane.**

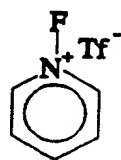
Reaction between 2,4-dimethyl-3-pentanone (1.2.4.3), trimethylsilyl chloride, and base gave 2,4-dimethyl-3-trimethylsilyloxy-2-pentene (1.2.4.4) which was reacted with 1-fluoropyridinium triflate (1.2.4.5) to form 2,4-dimethyl-2-fluoro-3-pentanone (1.2.4.6). This product was reacted with  $(\text{CH}_3)_3\text{S}(\text{O})^+\text{I}^-$  to form the title compound (1.2.4.2).



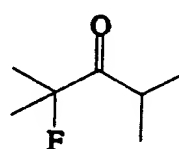
1.2.4.3



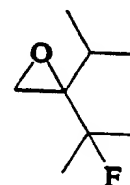
1.2.4.4



1.2.4.5



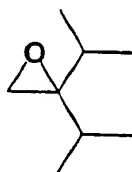
1.2.4.6



1.2.4.2

**1.2.4.7 2,2-Bis-isopropyl oxirane.**

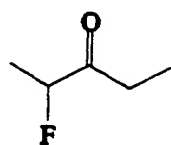
(From 2,4-dimethylpentanone using  $(\text{CH}_3)_3\text{S}(\text{O})^+\text{I}^-$  as described in 1.2.4.2)



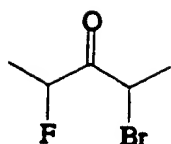
1.2.4.7

**1.2.4.8 2-(1-Fluoroethyl)-2-(1-trimethylsilyloxyethyl) oxirane.**

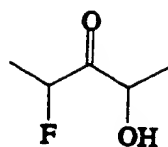
The title compound was obtained in several steps. DEK was O-silylated using usual procedure. The resulting product was reacted with 1-fluoropyridinium triflate (1.2.4.5) to yield 2-fluoro-3-pentanone (1.2.4.9). After bromination the 2-bromo-4-fluoro-3-pentanone (1.2.4.10) which was obtained was reacted with liquid ammonia to form 2-fluoro-4-hydroxy-3-pentanone (1.2.4.11). The free hydroxyl group was protected with trimethylsilylchloride to form 2-fluoro-4-trimethylsilyloxy-3-pentanone (1.2.4.12). This product was reacted with trimethylsulfoxonium iodide to form the title compound (1.2.4.8).



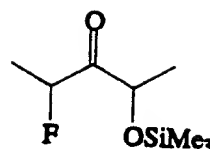
1.2.4.9



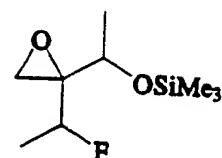
1.2.4.10



1.2.4.11



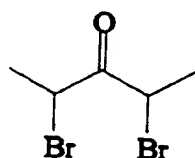
1.2.4.12



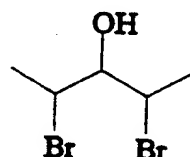
1.2.4.8

#### 1.2.4.13 2-(1-Bromoethyl)-3-methyl oxirane.

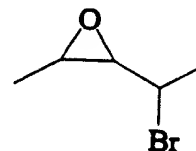
5 Bromination of diethyl ketone with bromine gave 2,4-dibromo-3-pentanone (1.2.4.14). This product was reduced with  $\text{BH}_3/\text{THF}$  to form 3-hydroxy-2,4-dibromopentane (1.2.4.15). After treatment with base the title compound (1.2.4.13) was obtained.



1.2.4.14



1.2.4.15



1.2.4.13

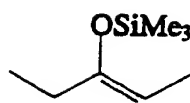
#### 10 1.2.4.16 2-(1-Fluoroethyl)-3-methyl oxirane.

From reaction between diethylketone and trimethylchlorosilane to form 3-trimethylsilyloxy-2-pentene (1.2.4.17). This product was reacted with 1-fluoropyridinium triflate (1.2.4.5) to obtain 2-fluoro-3-pentanone (1.2.4.9). After bromination with pyridinium bromide followed by reduction using diborane 2-fluoro-4-bromopentane-3-ol (1.2.4.18) was obtained. Reaction of this product with sodium methylate yielded the title compound (1.2.4.16). This compound was made also by reacting 2-(1-bromoethyl)-3-methyl oxirane (1.2.4.13) with  $\text{HF}/\text{Py}$  (70%) followed by treatment of the resulting 2-bromo-4-fluoropentan-3-ol (1.2.4.18) with  $\text{K}_2\text{CO}_3/\text{MeOH}$ .

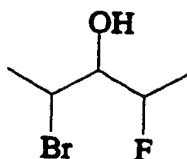
20

#### 1.2.4.19 2-(1-Fluoroethyl)-2-(1-methoxyethyl) oxirane.

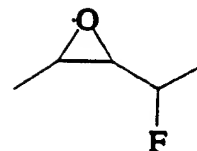
33



1.2.4.17

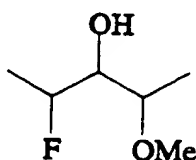


1.2.4.18

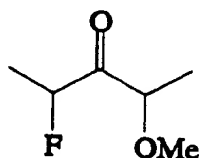


1.2.4.16

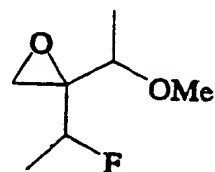
- 5 2-(1-Fluoroethyl)-3-methyl oxirane (1.2.4.16) was reacted with methanol/sulfuric acid to obtain 2-fluoro-4-methoxypentane-3-ol (1.2.4.20). This product was reacted with chromic anhydride/pyridine to form 2-fluoro-4-methoxypentane-3-one (1.2.4.21) which was then reacted with sodium hydride and trimethylsulfoxonium iodide to obtain the title compound (1.2.4.19).



1.2.4.20



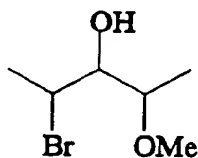
1.2.4.21



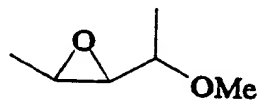
1.2.4.19

- 10 1.2.4.22 2-(1-Methoxyethyl)-3-methyl oxirane.

Reaction of 2-(1-Bromoethyl)-3-methyl oxirane (1.2.4.13) with methanol/sulfuric acid formed 2-bromo-3-hydroxy-4-methoxypentane (1.2.4.23). This product was reacted with potassium carbonate in methanol to obtain the title compound (1.2.4.22).



1.2.4.23



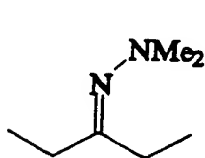
1.2.4.22

15

- 1.2.4.24 2-Ethyl-2-(1-methoxyethyl) oxirane.

Reaction between diethyl ketone and dimethyl hydrazine gave diethyl ketone-N,N-dimethylhydrazone (1.2.4.25). This product was reacted

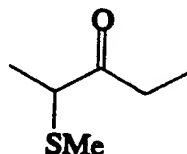
with dimethyl disulfide/LDA to obtain 2-methylthio-3-pentanone-N,N-dimethyl hydrazone (1.2.4.26). This product was reacted with mercuric chloride followed by cupric chloride to obtain 2-methoxy pentane-3-one (1.2.4.27). Reaction of the latter compound with sodium hydride/DMSO/trimethylsulfonium iodide yielded the title compound (1.2.4.24).



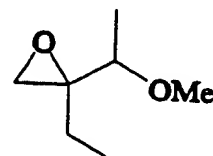
1.2.4.25



1.2.4.26



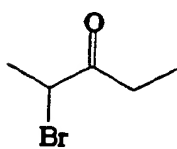
1.2.4.27



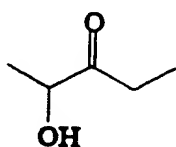
1.2.4.24

#### 1.2.4.28 2-Ethyl-2-(1-trimethylsilyloxyethyl) oxirane.

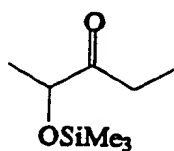
From reaction between 2-bromo-3-pentanone (1.2.4.29) and hydrazine obtained 2-hydroxy-3-pentanone (1.2.4.30). This product was reacted with trimethylchlorosilane/triethylamine to obtain 2-trimethylsilyloxy-3-pentanone (1.2.4.31). This product was reacted with methylenetriphenyl phosphite and butyllithium to obtain 2-ethyl-3-trimethylsilyloxy-1-butene (1.2.4.32). After oxidation with *meta*-chloroperbenzoic acid in methylene chloride the title compound (1.2.4.28) was obtained.



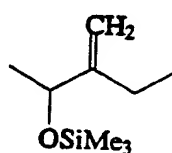
1.2.4.29



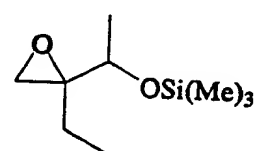
1.2.4.30



1.2.4.31



1.2.4.32

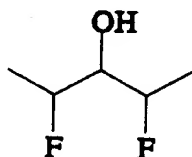


1.2.4.28

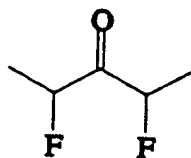
#### 1.2.4.33 2,2-Bis(1-fluoroethyl) oxirane.

From reaction between 2-(1-Bromoethyl)-3-methyl oxirane (1.2.4.13) and HF/pyridine was obtained 2-bromo-4-fluoro-pentane-3-ol (1.2.4.18). This was reacted with potassium carbonate to obtain 2-(1-fluoroethyl)-3-methyl oxirane (1.2.4.16). This was reacted again with HF/pyridine to obtain 2,4-difluoro-pentane-3-ol (1.2.4.34). After oxidation with

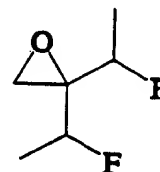
chromium trioxide obtained 2,4-difluoro-3-pentanone (1.2.4.35). The epoxide title compound was prepared from the ketone as described for 1.2.4.24.



1.2.4.34



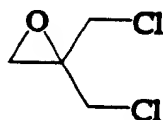
1.2.4.35



1.2.4.33

5      1.2.3.36      2,2-Bis-dichloromethyleneoxirane.

(From direct epoxidation of 3-chloro-2-chloromethyl-1-propene).



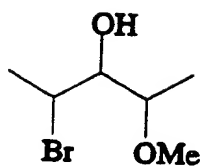
1.3.4.36

1.2.4.37      2,2-Bis(1-methoxyethyl) oxirane.

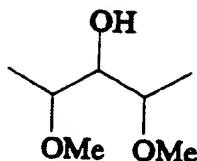
10      3-Pentanone was brominated to get 2,4-dibromo-3-pentanone (1.2.4.11) using conventional methods. The dibromoketone was reduced with  $\text{BH}_3 \cdot \text{THF}$  to the corresponding alcohol (1.2.4.15). This compound was reacted with  $\text{MeONa}$  in methanol to yield 2-(1-bromoethyl)-3-methyl oxirane (1.2.4.13) which after reaction with  $\text{MeOH}/\text{H}_2\text{SO}_4$  gave 2-bromo-3-hydroxy-4-methoxy pentane (1.2.4.38). This intermediate was reacted again with  $\text{MeONa}$  in methanol and the resulting 2-(1-methoxyethyl)-3-methyl oxirane (1.2.4.22) was reacted again with  $\text{MeOH}/\text{H}_2\text{SO}_4$  to yield 2,4-dimethoxy-3-hydroxy pentane (1.2.4.39). After oxidation with  $\text{CrO}_3/\text{Py}$  in methylenechloride the resulting ketone was reacted with trimethylsulfoxonium iodide to give the title compound (1.2.4.37).

15

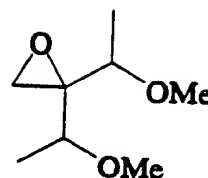
20



1.2.4.38



1.2.4.39



1.2.4.37

### 1.2.5 Phosphite and Alkyl Phosphonate Esters.

Dialkylphosphites were prepared by reacting diethylphosphite with the corresponding alcohol.

1.2.5.1 Di-n-butylphosphite,  $\text{HP(O)[OCH}_2(\text{CH}_2)_2\text{CH}_3]_2$   
(From n-butyl alcohol)

1.2.5.2 Dioctylphosphite,  $\text{HP(O)[OCH}_2(\text{CH}_2)_6\text{CH}_3]_2$ .  
(From octyl alcohol)

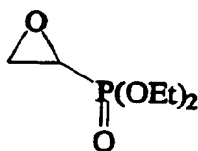
1.2.5.3 Diisobutylphosphite,  $\text{HP(O)(O}^i\text{Bu)}_2$ .  
(From iso butyl alcohol)

1.2.5.4 Dibenzyl phosphite,  $\text{HP(O)(OCH}_2\text{Ph)}_2$ .  
(From benzyl alcohol).

1.2.5.5 Diethyl(2-bromoethyl) phosphonate,  $\text{BrCH}_2\text{CH}_2\text{P(O)(OEt)}_2$ .  
(From reaction between triethylphosphite and 1,2-dibromethane)

1.2.5.6 Diethyl(2-chloro-1-hydroxyethyl) phosphonate,  
 $\text{ClCH}_2\text{CH(OH)P(O)(OEt)}_2$ .  
(From reaction of diethylphosphite and chloroacetaldehyde).

1.2.5.7 2-(Diethylphosphonate) oxirane.  
(From 1.2.5.6, sodium ethoxide).



1.2.5.7

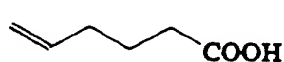
### 1.2.6 Halides and Tosylates

1.2.6.1 1-Bromo-2-hydroxy-3,3-dimethylbutane,  $\text{BrCH}_2\text{CH(OH)C(CH}_3)_2$   
(From reduction of bromomethyl-t-butyl ketone by  $\text{BH}_3/\text{THF}$ ).

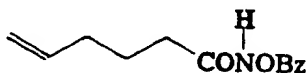
**1.2.6.2** 1-Bromo-2-t-butyldimethylsilyloxyethane,  $\text{BrCH}_2\text{CH}_2\text{Si}(\text{t-Bu})(\text{CH}_3)_2$   
(From bromoethanol and dimethyl-t-butylsilylchloride)

**1.2.6.3** 5-(p-Toluenesulfonyloxymethylene)-1-benzyloxy-2-pyrrolidone.

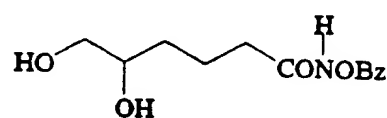
This compound was prepared in several steps. 4-pentenoic acid (1.2.6.4) was reacted with ethylchloroformate in the usual way to obtain the active mixed anhydride. To a solution of the mixed anhydride in chloroform was added triethylamine and O-benzylhydroxylamine hydrochloride to obtain O-benzyl-4-pentenohydroxamic acid (1.2.6.5). The double bond was oxidized using osmium tetroxide/N-methylmorpholine oxide to give the diol (1.2.6.6). The terminal hydroxyl group was then protected with t-butyldimethylsilylchloride in the usual way to yield (1.2.6.7). The secondary hydroxyl group was tosylated using pyridine/p-toluenesulfonyl chloride. Cyclization of (1.2.6.8) to the corresponding pyrrolidone (1.2.6.9) was effected by using sodium carbonate in methanol. The protecting silyl group was removed by treatment with tetraethylammonium fluoride. The title compound (1.2.6.3) was prepared by reacting the latter compound (1.2.6.10) with pyridine/p-toluenesulfonyl chloride in the usual way.



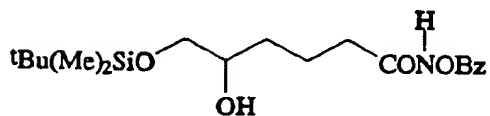
1.2.6.4



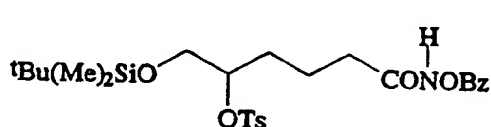
1.2.6.5



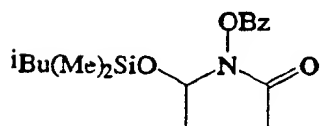
1.2.6.6



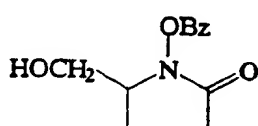
1.2.6.7



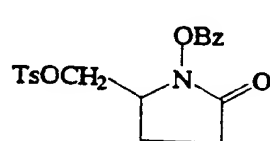
1.2.6.8



1.2.6.9



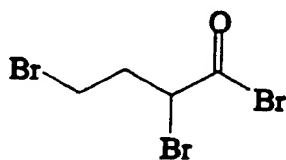
1.2.6.10



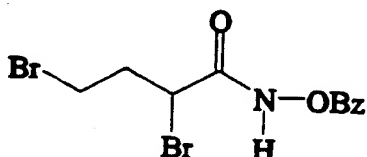
1.2.6.3

**1.2.6.11 5-Bromo-1-benzyloxy-2-pyrrolidone.**

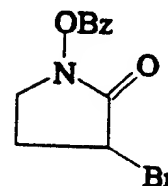
This compound was prepared in several steps. Butyrolactone was reacted with  $\text{PBr}_3/\text{Br}_2$  to obtain the dibromobutyrylbromide (1.2.6.12). This compound with O-benzylhydroxylamine yielded the protected dibromohydroxamic acid (1.2.6.13). Cyclization was effected by base to give the cyclic protected hydroxamic acid (1.2.6.11).



1.2.6.12



1.2.6.13



1.2.6.11

**1.2.7 Preparation of N-Alkyl-O-Benzylchloroacetohydroxamic Acids.**

This class of compounds was prepared from chloroacetyl chloride and the suitable N-Alkylhydroxylamine followed by O-benylation with benzyl bromide. In certain instances the O-benzyl alkylhydroxylamine was used as the starting material. O-Methyl chloroacetohydroxamic acid was prepared employing O-methylhydroxylamine as starting material.

**1.2.7.1 O-Benzyl-N-Methyl Chloroacetohydroxamic acid,**  
 $\text{ClCH}_2\text{CON}(\text{Me})(\text{OBz})$ .

**1.2.7.2 O-Benzyl-N-isopropyl-Chloroacetohydroxamic acid,**  
 $\text{ClCH}_2\text{CON}(\text{iPr})(\text{OBz})$ .

**1.2.7.3 O-Benzyl-N-tert-butyl-Chloroacetohydroxamic acid,**  
 $\text{ClCH}_2\text{CON}(\text{tBu})(\text{OBz})$ .

**1.2.7.4 O-Benzyl Chloroacetohydroxamic acid,**  $\text{ClCH}_2\text{CONH}(\text{OBz})$

**1.2.7.5 O-Methyl chloroacetohydroxamic acid,**  $\text{ClCH}_2\text{CONH}(\text{OMe})$

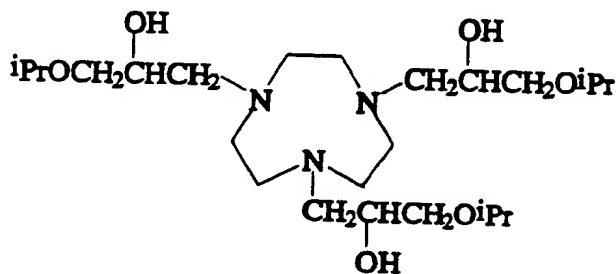
**1.3 SYNTHESIS OF CHELATORS (LIGANDS)****1.3.1 Synthesis of Polyaza Ligands with Pendant Arms Containing  $\beta$ -Hydroxy Groups and Their Derivatives.**

This family of compounds was prepared by reacting polyaza free bases with epoxides or halohydrines in water or alcohol solvents.

39

**1.3.1.1 N,N',N''-Tris (2-hydroxy-3-isopropoxypropyl)-1,4,7-Triazacyclononane.**

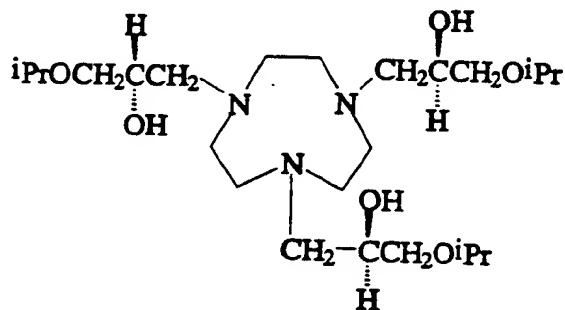
From 1,4,7-triazacyclononane (1.1.3) and d,l-glycidyl isopropyl ether (1.2.1.2).



1.3.1.1

**1.3.1.2 (R,R,R) N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and (2R) glycidyl isopropyl ether (1.2.1.3).

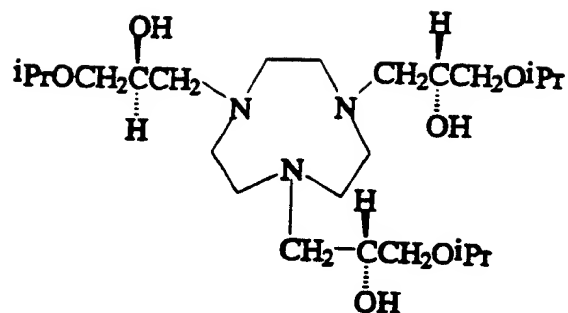


1.3.1.2

**1.3.1.3 (S,S,S) N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane.**

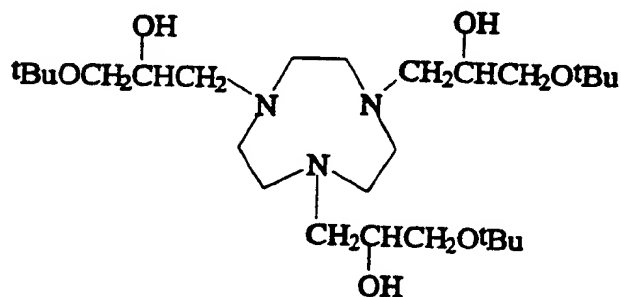
From 1,4,7-Triazacyclononane and (2S) glycidyl isopropyl ether (1.2.1.4).

40



1.3.1.3

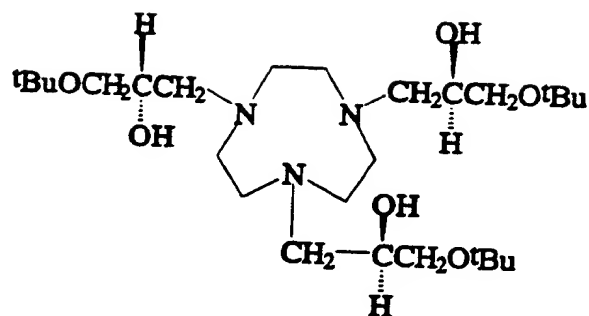
- 1.3.1.4** **N,N',N''-Tris(2-hydroxy-3-t-butoxypropyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-Triazacyclononane (1.13) and (d,l) glycidyl-t-Butyl ether  
 (1.2.1.5).



1.3.1.4

- 1.3.1.5** **(R,R,R) N,N',N''-Tris(2-hydroxy-3-t-butoxypropyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and (R) glycidyl t-Butyl ether  
 (1.2.1.6).

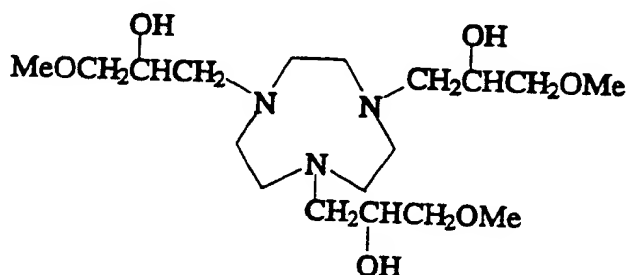
41



1.3.1.5

**1.3.1.6 N,N',N''-Tris(2-hydroxy-3-methoxypropyl)-1,4,7-triazacyclononane**

From 1,4,7-Triazacyclononane (1.1.3) and (d,l) glycidyl methyl ether (commercially available).

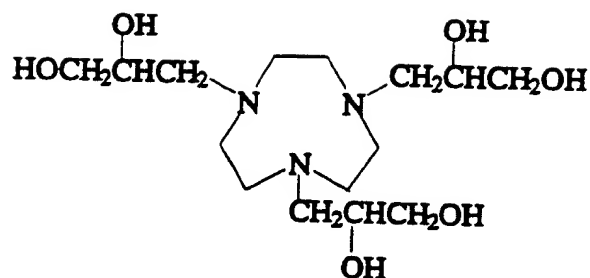


1.3.1.6

**1.3.1.7 N,N',N''-Tris(2,3-dihydroxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 1-bromo-2,3-dihydroxypropane (commercially available) and excess of potassium carbonate or 1-chloro-2,3-dihydroxypropane (commercially available) and base.

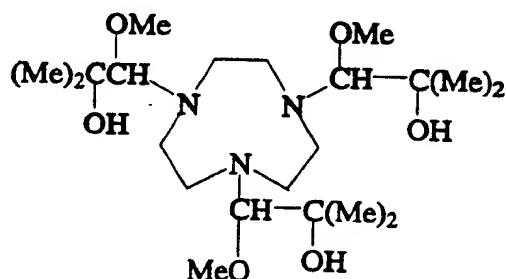
42



1.3.1.7

**1.3.1.8 N,N',N''-Tris(1-methoxy-2-hydroxy-2-methylpropyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and (d, l) 3,3-Dimethyl-2-methoxy oxirane (1-methoxy-2-methylpropylene, commercially available).

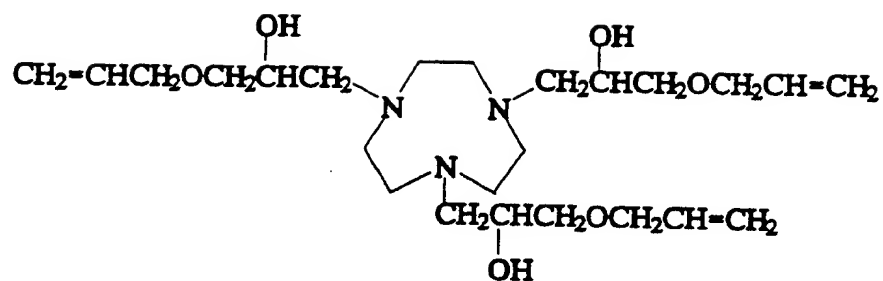


1.3.1.8

**1.3.1.9 N,N',N''-Tris(2-hydroxy-3-allyloxypropyl)-1,4,7-triazacyclononane.**

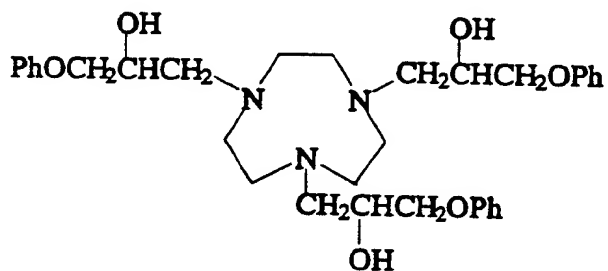
From 1,4,7-Triazacyclononane (1.1.3) and (d,l) glycidyl allyl ether (1.2.1.7).

43



1.3.1.9

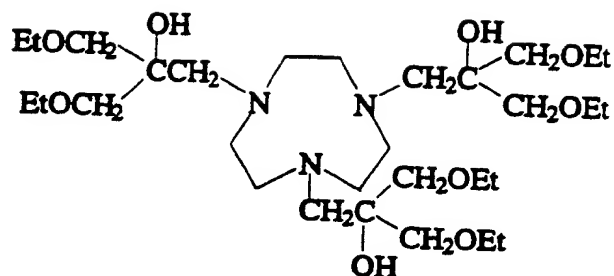
- 1.3.1.10** **N,N',N''-Tris(2-hydroxy-3-phenoxypropyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-Triazacyclononane (1.1.3) and (d,l) glycidyl phenyl ether (1.2.1.8).



1.3.1.10

- 1.3.1.11** **N,N',N''-Tris(2-hydroxy-2,2-diethoxymethylene)ethyl-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis-ethoxymethyl oxirane(1.2.2.1).

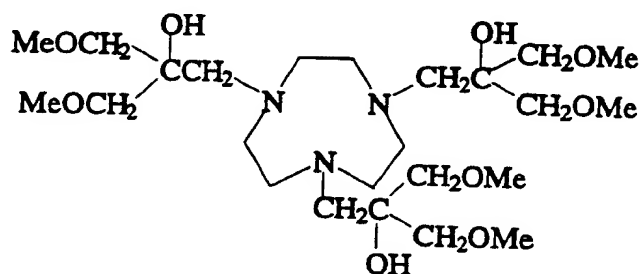
44



1.3.1.11

**1.3.1.12 N,N',N''-Tris(2-hydroxy-2,2-dimethoxymethyl)ethyl-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis-methoxyoxymethyl oxirane (1.2.2.2).

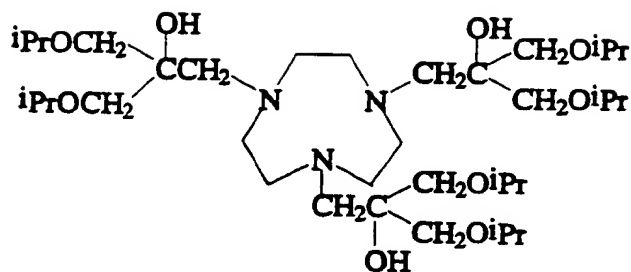


1.3.1.12

**1.3.1.13 N,N',N''-Tri(2-hydroxy-(2,2-diisopropyloxymethyl)ethyl-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis-isopropoxymethyl oxirane (1.2.2.3).

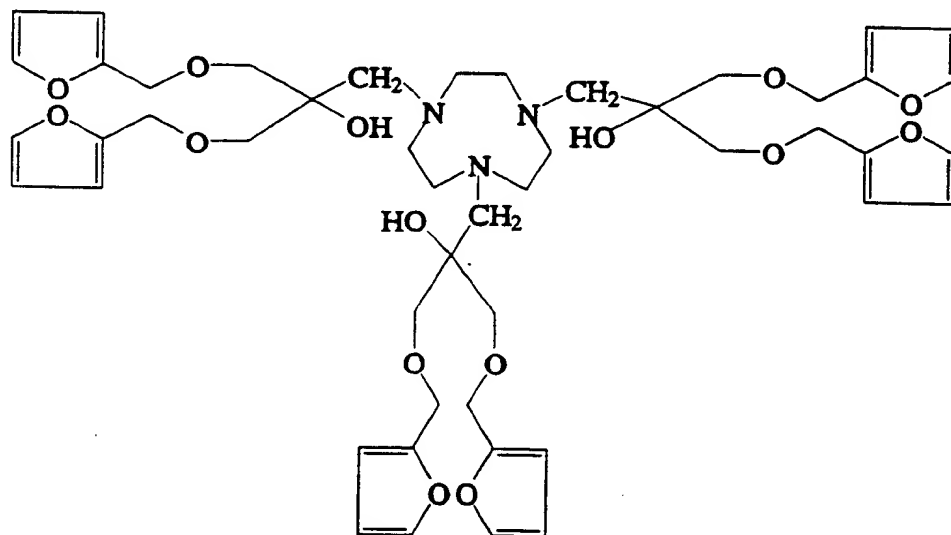
45



1.3.1.13

**1.3.1.14 N,N',N''-Tris[2-hydroxy-bis(2-furfuryloxymethyl)ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis(furfuryloxymethyl) oxirane (1.2.2.4).

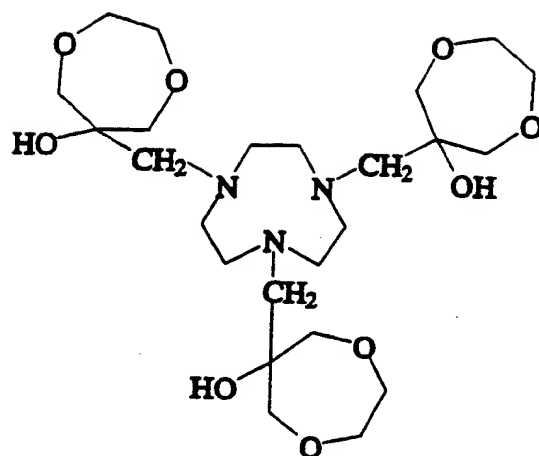


1.3.1.14

**1.3.1.15 N,N',N''-Tris(3-hydroxy-1,5-dioxacycloheptyl-3-methyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxacycloheptane) (1.2.3.1).

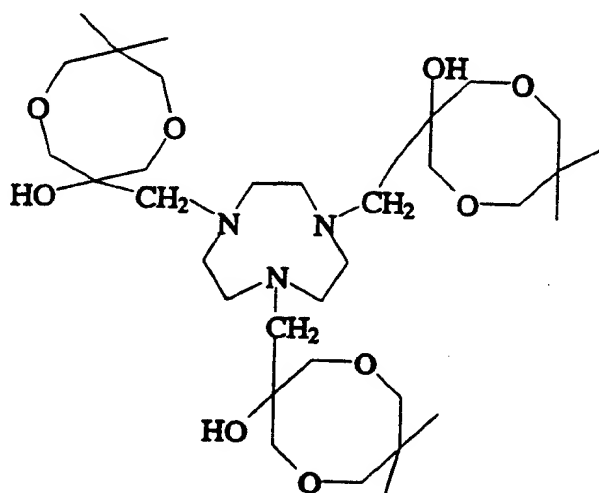
46



1.3.1.15

**1.3.1.16** **N,N',N''-Tris[(3-Hydroxy-7,7-dimethyl-1,5-dioxacyclooct-3-yl)-methyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxa-7,7-dimethylcyclooctane) (1.2.3.2).

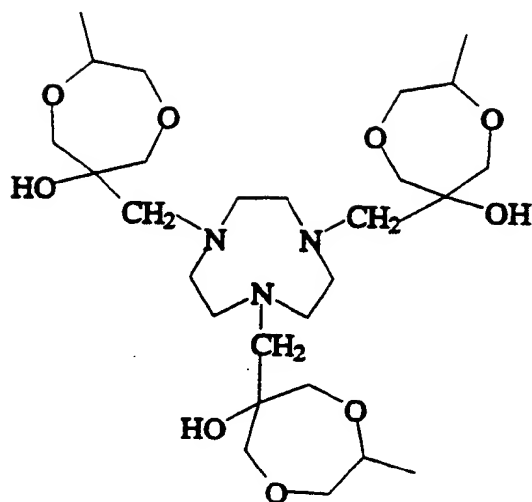


1.3.1.16

**1.3.1.17** **N,N',N''-Tris[(3-hydroxy-7-methyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and Oxiranespiro-3-(1,5-dioxa-6-methylcycloheptane) (1.2.3.3).

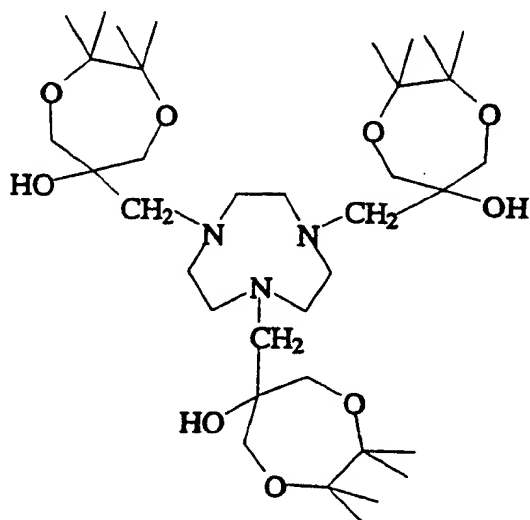
47



1.3.1.17

**1.3.1.18** **N,N',N''-Tris[(3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-Triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxa-6,6,7,7-tetramethylcycloheptane) (1.2.3.4).



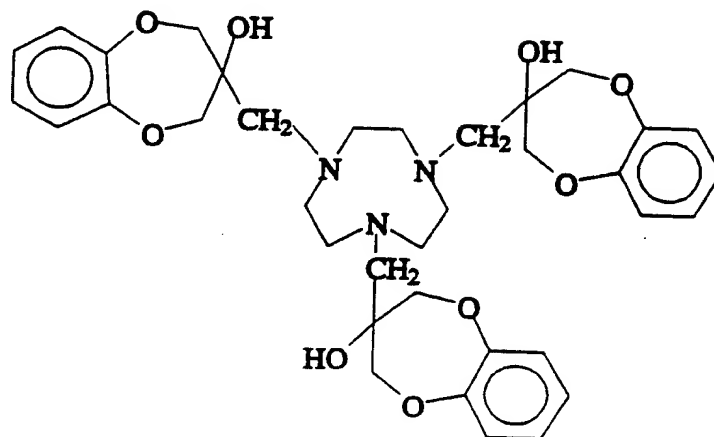
1.3.1.18

**1.3.1.19** **N,N',N''-Tris[(3-hydroxy-benzo[b]-1,5-dioxacycloheptyl)methyl]1,4,7-triazacyclononane.**

**SUBSTITUTE SHEET (RULE 26)**

48

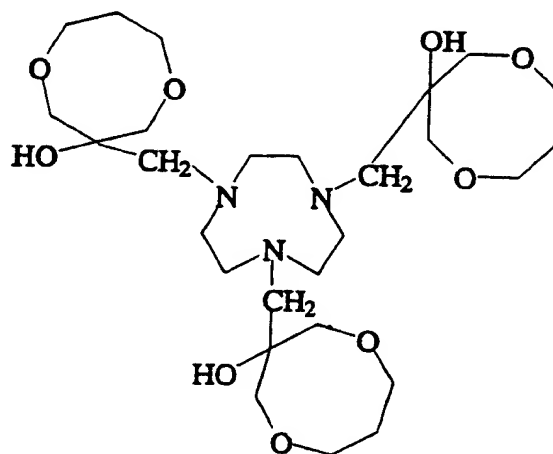
From 1,4,7-triazacyclononane (1.1.3) and oxiranespiro-3-(benzo[b]-1,5-dioxacycloheptane) (1.2.3.5).



1.3.1.19

**1.3.1.20** N,N',N''-Tris[(3-hydroxy-1,5-dioxacyclooctane-3-yl)methyl]-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxacyclooctane) (1.2.3.6).



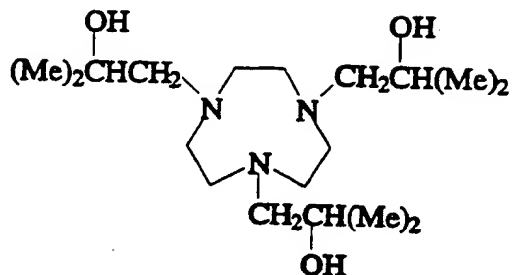
1.3.1.20

**1.3.1.21** N,N',N''-Tris(2-hydroxy-2-methylpropyl)-1,4,7-Triazacyclononane.

**SUBSTITUTE SHEET (RULE 26)**

49

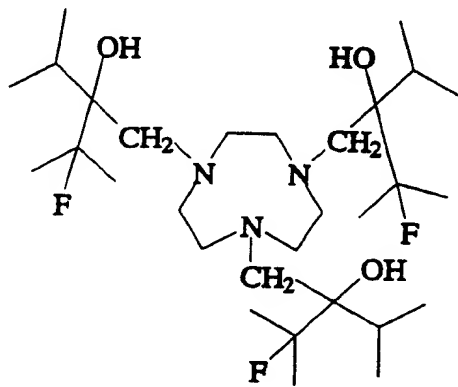
From 1,4,7-Triazacyclononane (1.1.3) and 2,2-Dimethyl oxirane (1.2.4.1)



1.3.1.21

**1.3.1.22** N,N',N''-Tris[(4-fluoro-2-hydroxy-3-i-propyl-4-methyl)pentyl]-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3) and 2-isopropyl-2-(1-fluoro-1-methylethyl) oxirane (1.2.4.2).

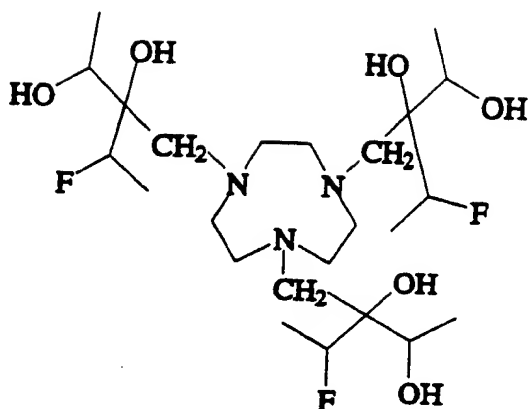


1.3.1.22

**1.3.1.23** N,N',N''-Tris-[2-hydroxy-3-(1-fluoroethyl)-4-hydroxypentyl]-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3) and 2-(1-trimethylsilyloxyethyl)-2-(1-fluoroethyl) oxirane (1.2.4.8).

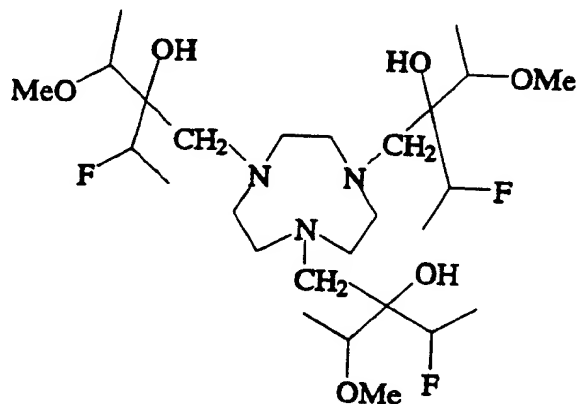
50



1.3.1.23

**1.3.1.24 N,N',N''-Tris[2-hydroxy-2-(1-fluoroethyl)-2-(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-(1-Fluoroethyl)-2-(1-methoxyethyl) oxirane (1.2.4.19).

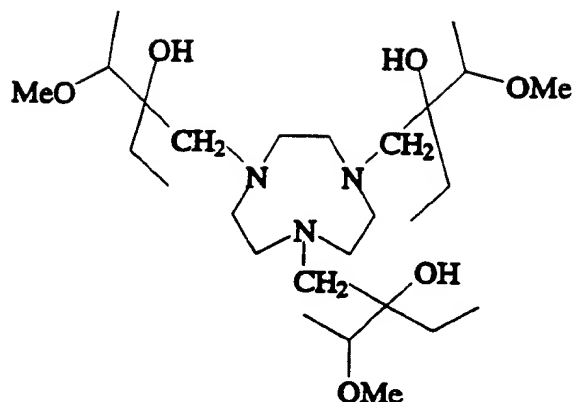


1.3.1.24

**1.3.1.25 N,N',N''-Tris(2-hydroxy-2-ethyl-3-methoxy butyl)-1,4,7-triazacyclononane.**

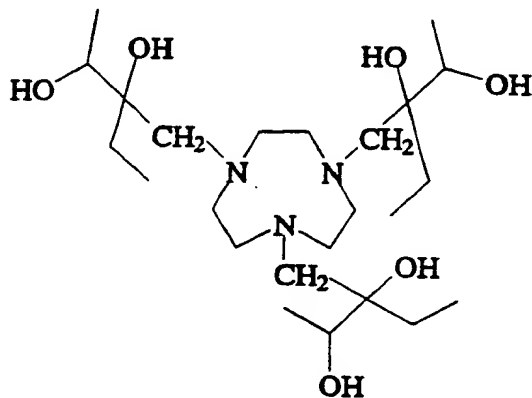
From 1,4,7-triazacyclononane (1.1.3) and 2-ethyl-2-(1-methoxyethyl) oxirane (1.2.4.24).

51



1.3.1.25

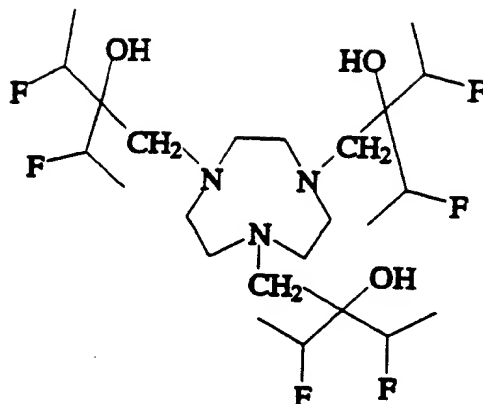
- 1.3.1.26** **N,N',N''-Tris(2,3-dihydroxy-2-ethyl)butyl]-1,4,7-Triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and 2-ethyl-2-(1-trimethylsilyloxyethyl) oxirane (1.2.4.28).



1.3.1.26

- 1.3.1.27** **N,N',N''-Tris[2-hydroxy-2,2-bis(1-fluoro ethyl) ethyl]-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and 2,2-bis(1-fluoroethyl) oxirane (1.2.4.33):

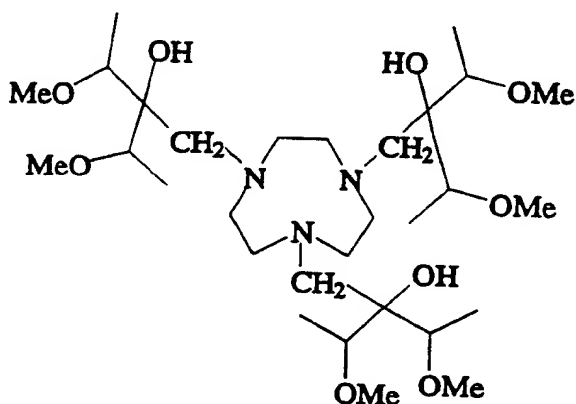
52



1.3.1.27

**1.3.1.28** *N,N',N''*-Tris[2-hydroxy-2,2-bis(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane.

From 1,4,7-Triazacyclononane (1.1.3) and 2,2-(1-methoxyethyl)oxirane (1.2.4.37).

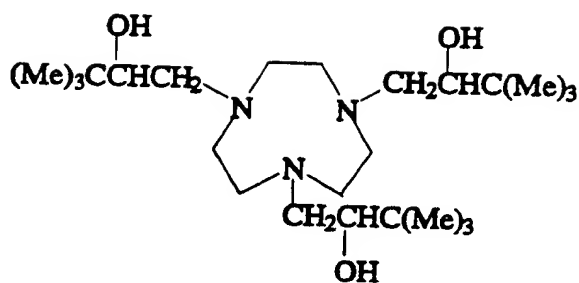


1.3.1.28

**1.3.1.29** *N,N',N''*-Tris[(3,3-dimethyl-2-hydroxy)butyl]-1,4,7-triazacyclononane.

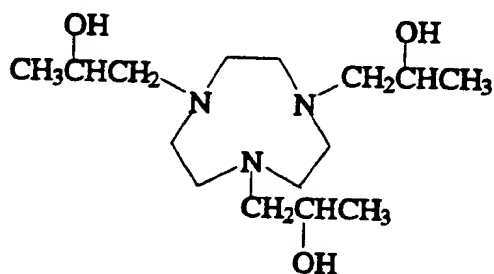
From 1,4,7-Triazacyclononane (1.1.3), 1-Bromo-2-hydroxy-3,3-dimethylbutane (1.2.6.1) and sodium carbonate.

53



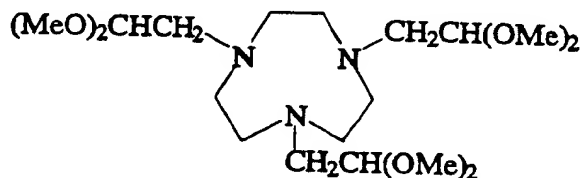
1.3.1.29

- 1.3.1.30**    **N,N',N''-Tris(2-hydroxypropyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and propylene oxide.



1.3.1.30

- 1.3.1.31**    **N,N',N''-Tris(2,2-dimethoxyethyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3), 1-chloro-2,2-dimethoxyethane (commercially available) and sodium carbonate.

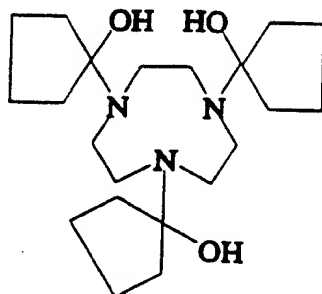


1.3.1.31

- 1.3.1.32**    **N,N',N''-Tris(2-hydroxycyclopentan-1-yl)-1,4,7-triazacyclononane.**

54

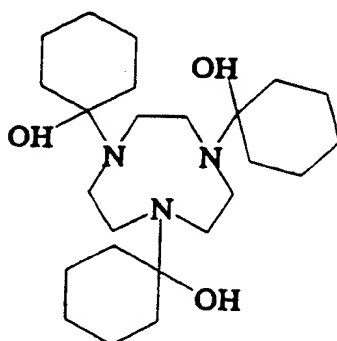
From 1,4,7-triazacyclononane (1.1.3), 1,2-epoxycyclopentane (commercially available) and sodium carbonate.



1.3.1.32

**1.3.1.33**    **N,N',N''-Tris(2-hydroxycyclohexane-1-yl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), 1,2-epoxycyclohexane (commercially available) and sodium carbonate.

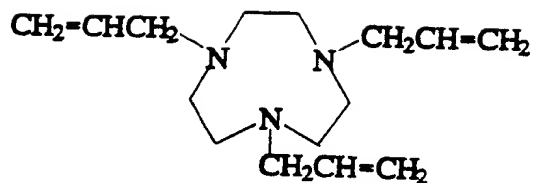


1.3.1.33

**1.3.1.34**    **N,N',N''-Triallyl-1,4,7-Triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), sodium hydride and allyl bromide.

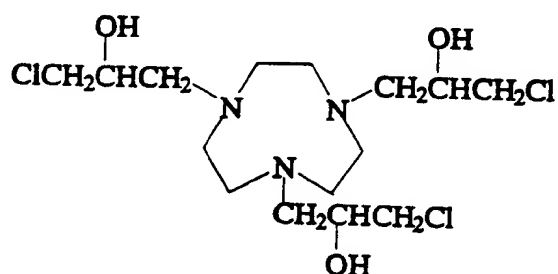
55



1.3.1.34

**1.3.1.35** **N,N',N''-Tris[(3-chloro-2-hydroxy)propyl]-1,4,7-Triazacyclononane.**

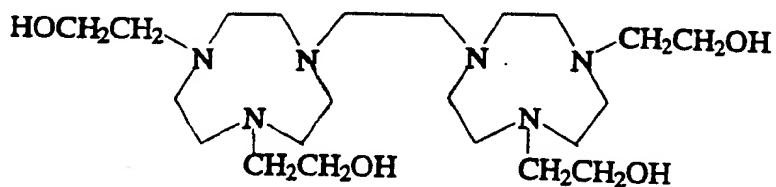
From N,N',N''-triallyl-1,4,7-triazacyclononane(1.3.1.34) and aqueous chlorine.



1.3.1.35

**1.3.1.36** **1,2-Bis-(N,N'-di-2-hydroxyethyl-1,4,7-triazacyclononane-1-yl) ethane.**

From 1,2-bis-(1,4,7-triazacyclononane-1-yl) ethane polyhydrobromide and ethylene oxide.

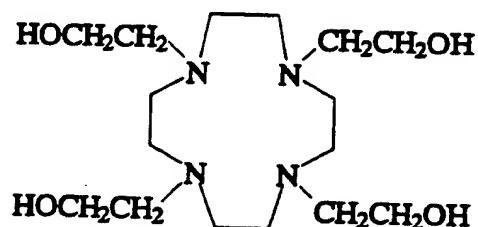


1.3.1.36

56

**1.3.1.37    N,N',N'',N'''-Tetrakis-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane.**

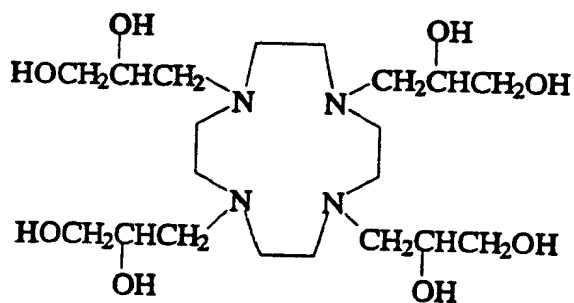
From 1,4,7,10-Tetraazacyclododecane (1.1.4) and bromoethanol.



1.3.1.37

**1.3.1.38    N,N',N'',N'''-Tetrakis(2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclotetradecane.**

From 1,4,7,10-tetraazacyclotetradecane (1.1.4), 1-chloro-2,3-propanediol (commercially available) and base.

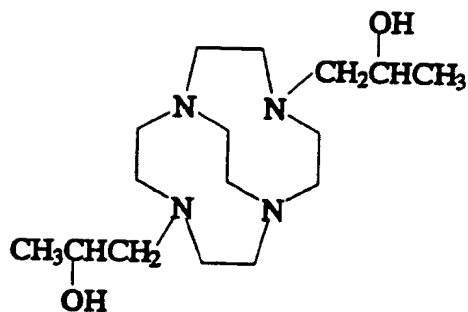


1.3.1.38

**1.3.1.39    4,10-Bis(2-Hydroxypropyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.4) and propylene oxide.

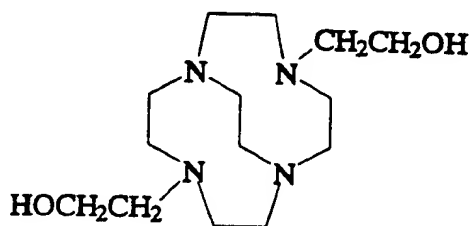
57



1.3.1.39

**1.3.1.40** 4,10-Bis-(2-hydroxyethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.

From 4,10-Bis(dimethoxycarbonylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.6.8) and lithium aluminum hydride.

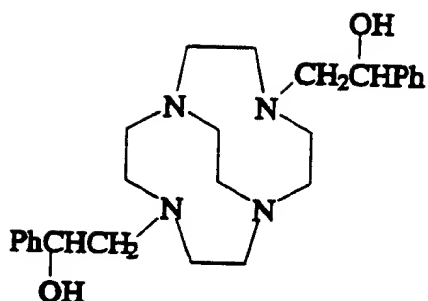


1.3.1.40

**1.3.1.41** 4,10-Bis[(2-Hydroxy-2-phenyl)ethyl]-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.

From 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (1.1.4) and styrene oxide.

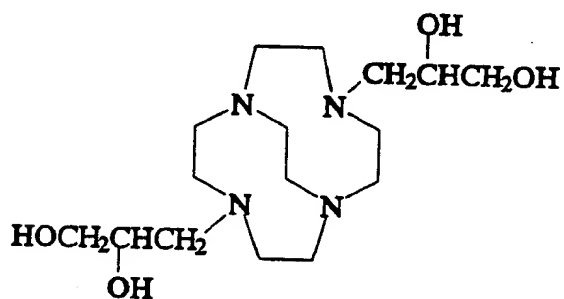
58



1.3.1.41

**1.3.1.42 4,10-Bis-(2,3-dihydroxypropyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

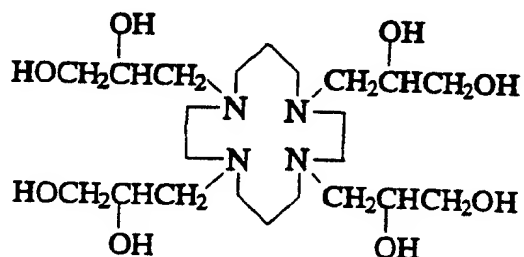
From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.4) and glycidol.



1.3.1.42

**1.3.1.43 N,N',N'',N'''-Tetrakis-(2,3-dihydroxypropyl)-1,4,8,11-tetraazacyclohexadecane.**

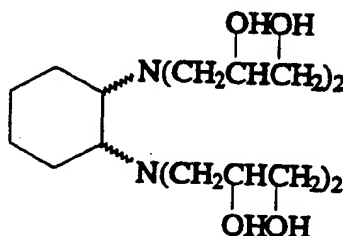
From cyclam (1.1.5) and glycidol.



1.3.1.43

**1.3.1.44** *cis, trans N,N,N',N'*-Tetrakis(2,3-dihydroxypropyl)-1,2-diamino-cyclohexane.

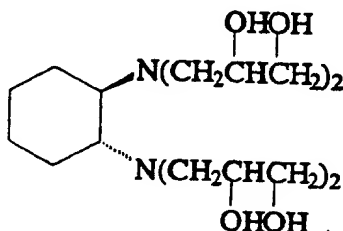
From *cis,trans* 1,2-diaminocyclohexane (commercially available) and glycidol.



1.3.1.44

**1.3.1.45** *trans N,N,N',N'*-Tetrakis(2,3-dihydroxypropyl)-1,2-diamino-cyclohexane.

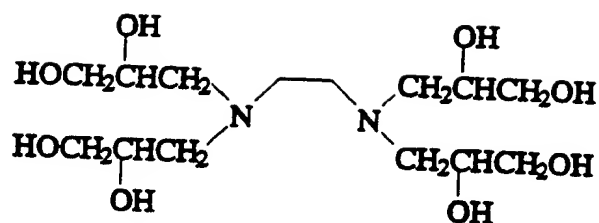
From *trans*-1,2-diaminocyclohexane (commercially available) and glycidol.



1.3.1.45

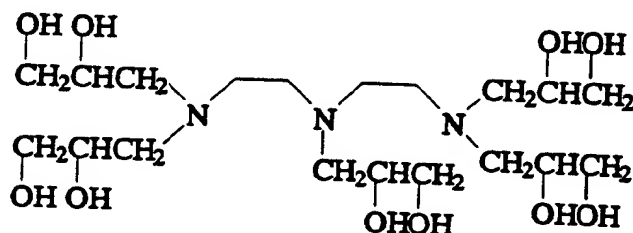
**1.3.1.46** *N,N,N',N'*-Tetrakis(2,3-dihydroxypropyl)-ethylenediamine.

From ethylenediamine (1.1.0) and glycidol.



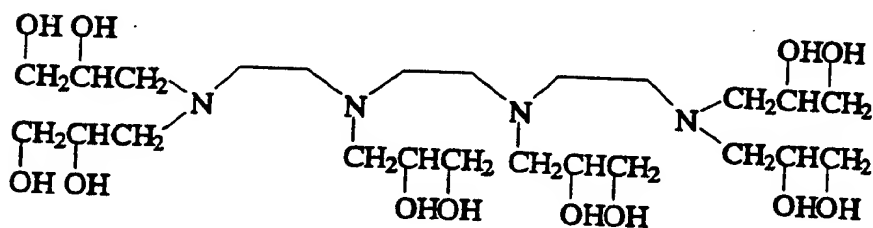
1.3.1.46

- 1.3.1.47** **N,N,N',N'',N'''-Pentakis(2,3-dihydroxypropyl)-diethylenetriamine.**  
From diethylenetriamine (1.1.1), 1-chloro-2,3-propanediol and base.



1.3.1.47

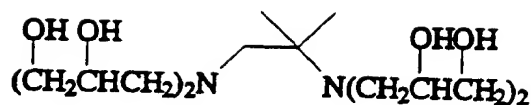
- 1.3.1.48** **N,N,N',N'',N''',N'''-Hexakis(2,3-dihydroxypropyl)triethylenetetramine.**  
From triethylenetetramine (1.1.2) and glycidol.



1.3.1.48

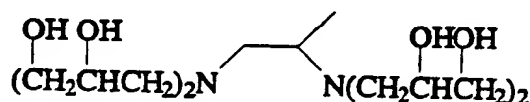
- 1.3.1.49** **N,N,N',N'-Tetrakis(2,3-dihydroxypropyl)-1,2-diamino-2-methylpropane.**  
From 1,2-diaminomethylpropane and glycidol.

61



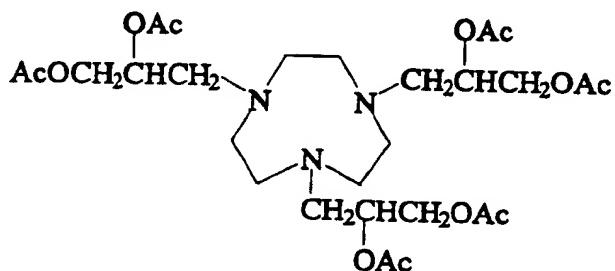
1.3.1.49

- 1.3.1.50** **N,N,N',N'-Tetrakis(2,3-dihydroxypropyl)-1,2-diaminopropane.**  
From 1,2-diaminopropane and glycidol.



1.3.1.50

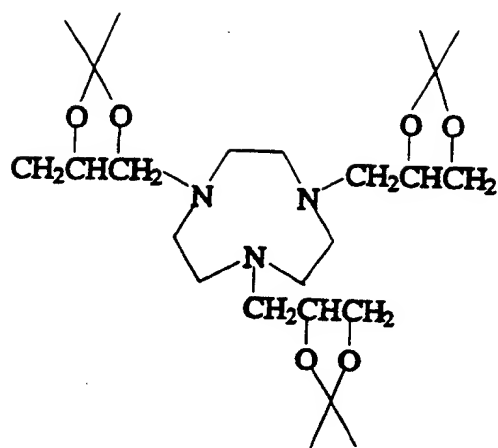
- 1.3.1.51** **N,N',N''-Tris(2,3-diacetoxypropyl)-1,4,7-triazacyclononane.**  
From 1.3.1.7 and Py/Ac<sub>2</sub>O.



1.3.1.51

- 1.3.1.52** **N,N',N''-tris(Dimethyl-2,3-isopropylidene propyl)-1,4,7-triazacyclononane.**  
From 1.3.1.7 and 2,2-dimethoxypropane/p-toluenesulfonic acid.

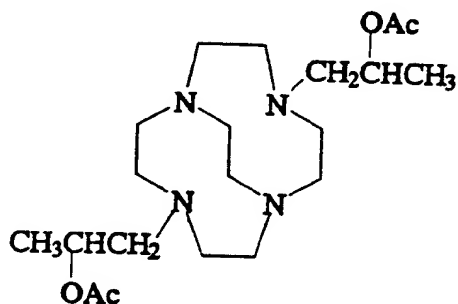
62



1.3.1.52

**1.3.1.53** 4,10-(2-Diacetoxypentyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.

From 1.3.1.39 and Py/Ac<sub>2</sub>O.

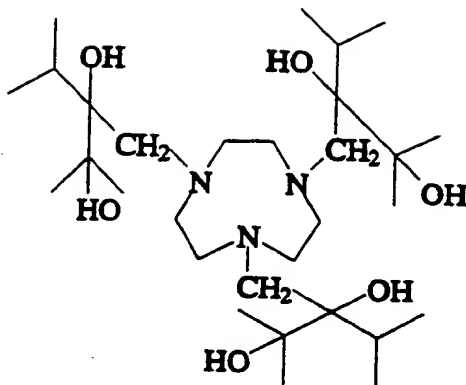


1.3.1.53

**1.3.1.54** N,N',N''-Tris[(2,4-dihydroxy-3-isopropyl-4-methyl)pentyl]-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3) and 2,2-bis(hydroxymethyl) oxirane.

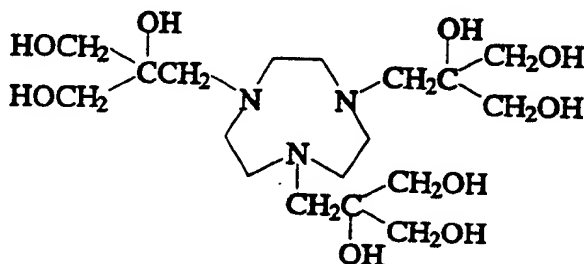
63



1.3.1.54

**1.3.1.55    *N,N',N''*-Tris-[2-hydroxy-(2,2-dihydroxymethyl)ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-bis(hydroxymethyl)oxirane (1.2.2.5).



1.3.1.55

**1.3.2        Synthesis of Polyaza Ligands With Alkylphosphonate Mono- and Di-Esters Pendant Arms.**

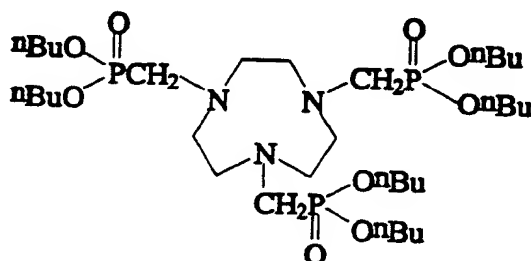
**1.3.2.1      Preparation**

Chelators which have three identical methylene phosphonate diester arms were prepared by reacting the trihydrobromide polyaza bases with formaldehyde and dialkylphosphite. The hexa-ester was hydrolized to the tri-

ester by heating with NaOH dissolved in the appropriate alcohol (the same R group as in the dialkylphosphite). In some cases products were obtained by reacting the amine base with haloalkylphosphonates or epoxyphosphonates.

**1.3.2.1 N,N',N''-Tris(dibutylphosphorylmethyl)-1,4,7-triazacyclononane.**

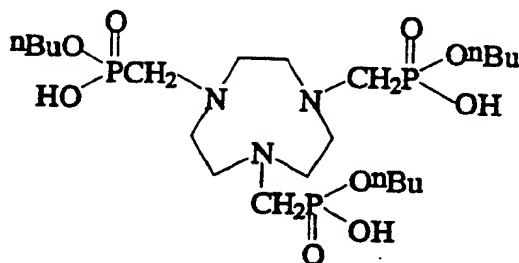
From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, formaldehyde solution and di-n-butyl phosphite (1.2.5.1).



1.3.2.1

**1.3.2.2 N,N',N''-Tris(dihydroxyphosphorylmethyl mono butyl ester)-1,4,7-triazacyclononane.**

From N,N',N''-tris(dibutylphosphorylmethyl)-1,4,7-triazacyclononane (1.3.2.1) and KOH/butanol.

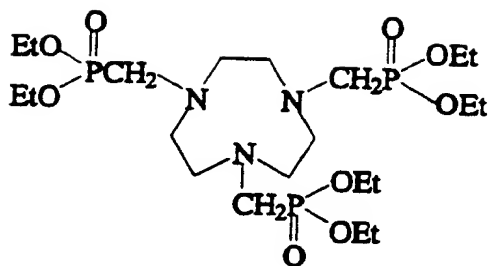


1.3.2.2

**1.3.2.3 N,N',N''-Tris(diethylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, formaldehyde solution and diethyl phosphite (commercially available).

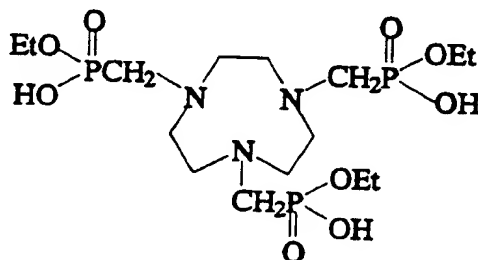
65



1.3.2.3

**1.3.2.4 N,N',N''-Tris(dihydroxyphosphorylmethyl monoethyl ester)-1,4,7-triazacyclononane.**

From N,N',N''-tris(diethylphosphorylmethyl)-1,4,7-triazacyclononane (1.3.2.3) and NaOH/EtOH.

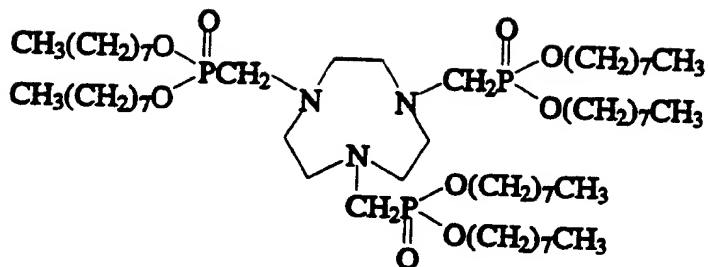


1.3.2.4

**1.3.2.5 N,N',N''-Tris(dioctylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), formaldehyde and dioctylphosphite (1.2.5.2).

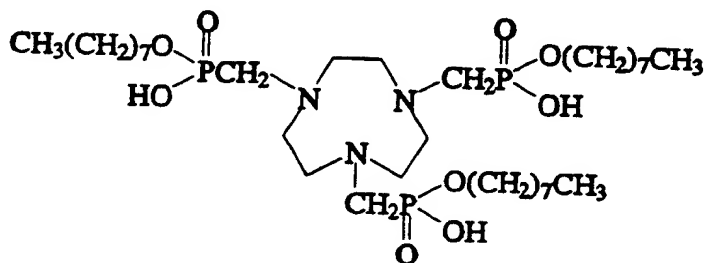
66



1.3.2.5

**1.3.2.6     N,N',N''-Tris(dihydroxyphosphorylmethyl mono-octyl ester)-1,4,7-triazacyclononane.**

From 1.3.2.5 and NaOH in octyl alcohol.

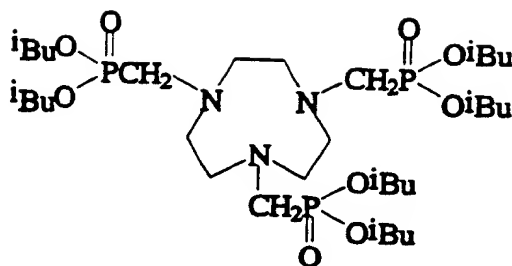


1.3.2.6

**1.3.2.7     N,N',N''-Tris(diisobutylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3), formaldehyde and diisobutylphosphite (1.2.5.3).

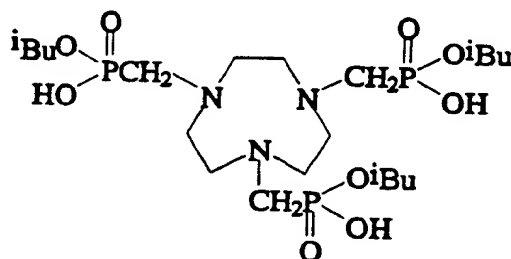
67



1.3.2.7

**1.3.2.8     N,N',N''-Tris(dihydroxyphosphorylmethyl monoisobutyl ester)-1,4,7-triazacyclononane.**

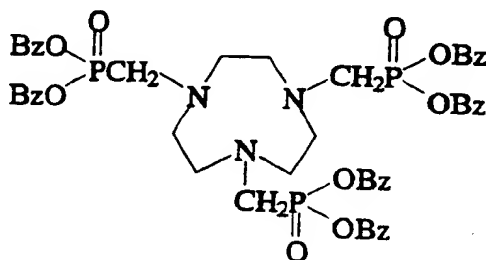
From 1.3.2.7 and NaOH in isobutyl alcohol.



1.3.2.8

**1.3.2.9     N,N',N''-Tris(dibenzylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3), formaldehyde and dibenzylphosphite (1.2.5.4).

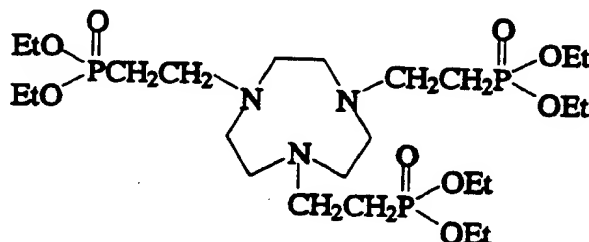


1.3.2.9

68

**1.3.2.10 N,N',N''-Tris(diethylphosphorylethyl)-1,4,7-triazacyclononane.**

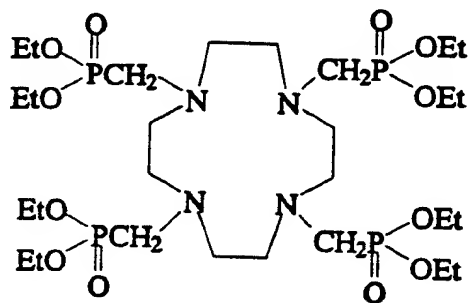
From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, potassium carbonate and diethyl(2-bromoethyl)phosphonate (1.2.5.5).



1.3.2.10

**1.3.2.11 N,N',N'',N'''-Tetrakis(diethylphosphorylmethyl)-1,4,7,10-Tetraazacyclodecane.**

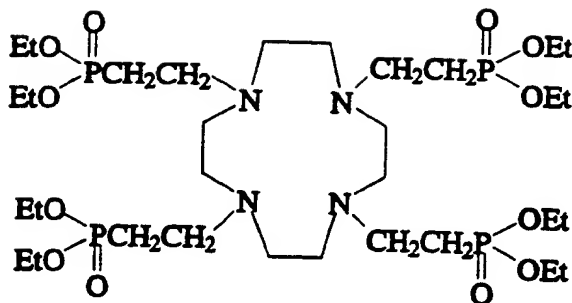
From 1,4,7,10-Tetraazacyclodecane (1.1.4) trihydrobromide, formaldehyde and diethylphosphite (commercially available).



1.3.2.11

**1.3.2.12 N,N',N'',N'''-Tetrakis(diethylphosphorylethyl)-1,4,7,10-tetraazacyclododecane.**

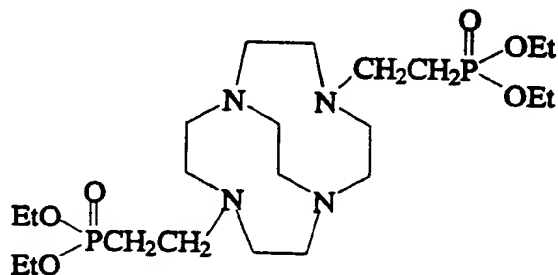
From 1,4,7,10-tetraazacyclododecane (1.1.4) trihydrobromide, potassium carbonate and diethyl(2-bromoethyl)phosphonate (1.2.5.5).



1.3.2.12

**1.3.2.13 4,10-Bis(diethylphosphoryl ethyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) dihydrobromide, potassium carbonate and diethyl(2-bromoethyl)phosphonate (1.2.5.5).

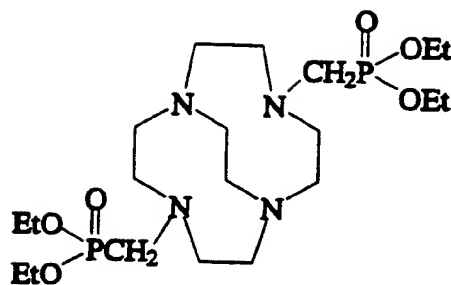


1.3.2.13

**1.3.2.14 4,10-Bis(diethylphosphoryl methyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) trihydrobromide, formaldehyde and diethylphosphite (commercially available).

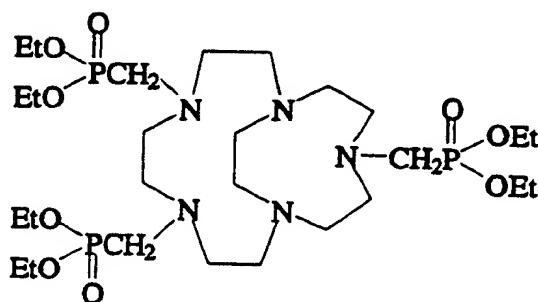
70



1.3.2.14

**1.3.2.15    N,N',N''-Tris(diethylphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane.**

From 1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.1.25), formaldehyde and diethylphosphite (commercially available).



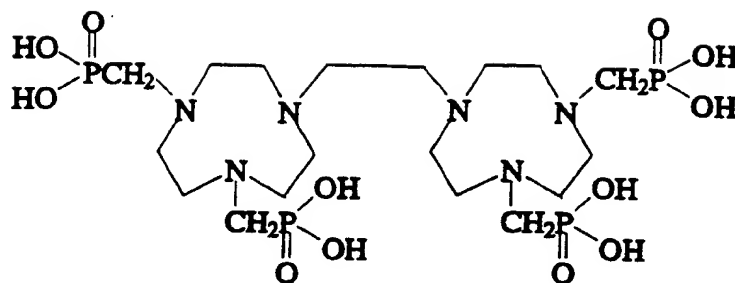
1.3.2.15

**1.3.3        Synthesis of Polyaza Ligands with Identical Alkylphosphonic Acid Pendant Arms.**

These compounds were prepared by either hydrolizing the ester groups of the compounds described under 1.3.2, or from the polyaza base, formaldehyde and phosphorous acid.

**1.3.3.1        1, 2-Bis(N,N'-bis(dihydroxyphosphrylmethyl)-1,4,7-triazacyclononan-1-yl) ethane.**

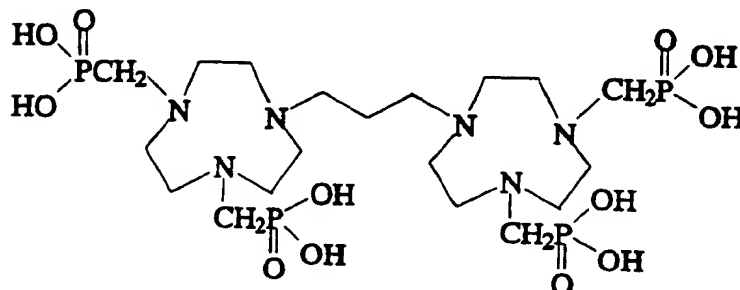
From 1,2-bis-(1,4,7-triazacyclononan-1-yl)ethane (1.1.28), formaldehyde and phosphorous acid.



1.3.3.1

**1.3.3.2**      **1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)propane.**

From 1,2-Bis-(1,4,7-triazacyclononan-1-yl)propane (1.1.19), formaldehyde and phosphorous acid.

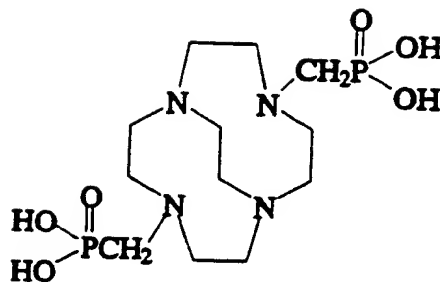


1.3.3.2

**1.3.3.3**      **4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (1.1.20) trihydrobromide, formaldehyde and phosphorous acid.

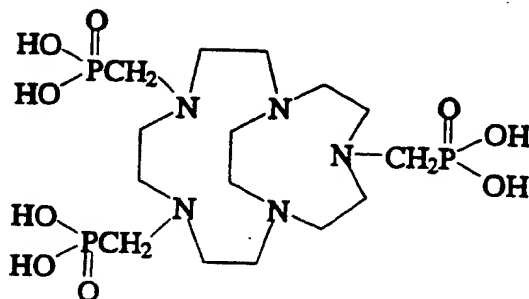
72



1.3.3.3

**1.3.3.4 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane.**

From hydrolysis of 1,4,7,13-tris(diethylphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.2.15) by HCl.

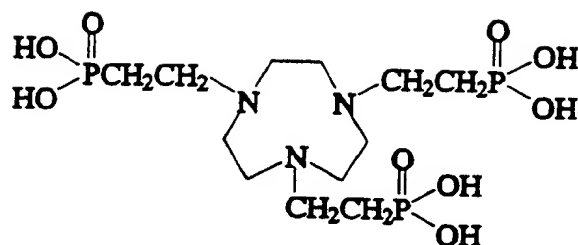


1.3.3.4

The following compounds were prepared from the corresponding diesters by hydrolysis with HCl:

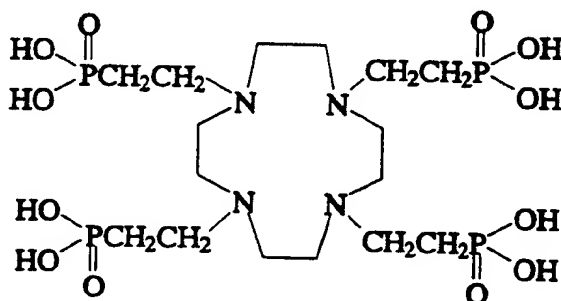
**1.3.3.5 N,N',N''-Tris(dihydroxyphosphorylethyl)-1,4,7-triazacyclononane.**

73



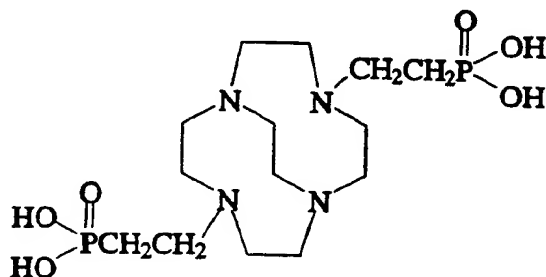
1.3.3.5

**1.3.3.6** **N,N',N'',N'''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane.**



1.3.3.6

**1.3.3.7** **4,10-Bis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**



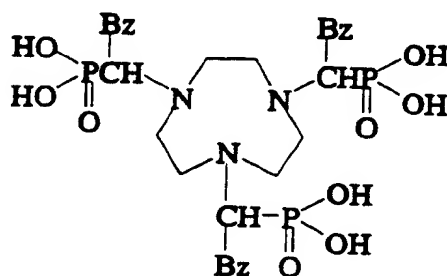
1.3.3.7

**1.3.4 Synthesis of Polyaza Ligands with Pendant Arms Containing Phosphonate Esters and Acids with Alpha Substituent Groups.**

Alkyl or aryl groups  $\alpha$  to the phosphonate moiety were prepared by alkylation of the corresponding ligand in the form of its dialkylphosphonate.

**1.3.4.1 N,N',N''-Tris[ $\alpha$ -dihydroxyphosphoryl- $\alpha$ -benzyl)methyl]-1,4,7-Triazacyclononane.**

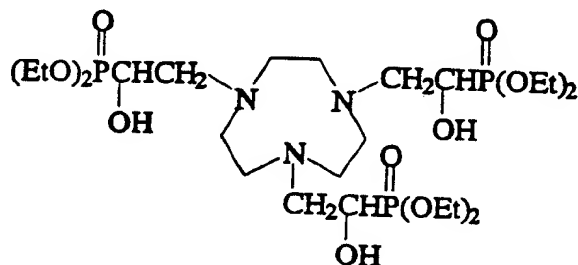
From N,N',N''-Tris[( $\alpha$ -diethylphosphoryl- $\alpha$ -benzyl)methyl]-1,4,7-triazacyclononane (US patent 5,380,515) and trimethylsilyl iodide.



1.3.4.1

**1.3.4.2 N,N',N''-Tris{[(diethylphosphoryl)- $\alpha$ -hydroxy]ethyl}-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-diethylphosphoryl oxirane (1.2.5.7).

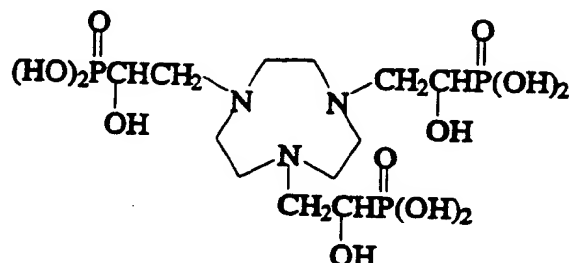


1.3.4.2

75

**1.3.4.3     N,N',N''-Tris[dihydroxyphosphoryl- $\alpha$ -hydroxy]ethyl]-1,4,7-triazacyclononane.**

From 1.3.4.2 and HCl.



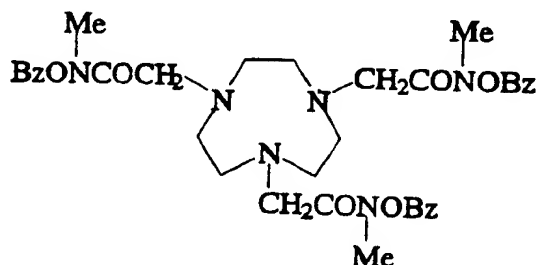
1.3.4.3

**1.3.5     Synthesis of Polyaza Ligands with Pendant Arms Containing Hydroxamate Groups.**

These compounds were prepared by reacting 1,4,7-tetraazacyclononane (1.1.3) trihydrobromide with a N-alkyl-O-benzyl chloroacetohydroxamic acid in the presence of a base. The free hydroxamic acid was obtained by removing the benzyl protecting group by hydrogenolysis.

**1.3.5.1     N,N',N''-Tris[(N-methyl-N-benzyloxycarbonyl)methyl]1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane, sodium carbonate and O-benzyl-N-methyl chloroacetohydroxamate (1.2.7.1).

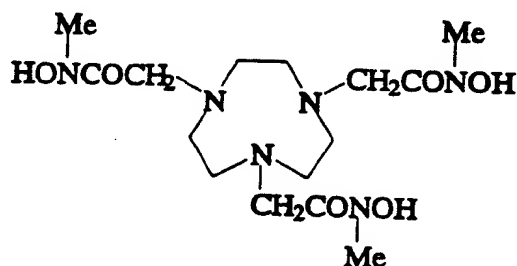


1.3.5.1

76

**1.3.5.2      N,N',N''-Tris[(N-methyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

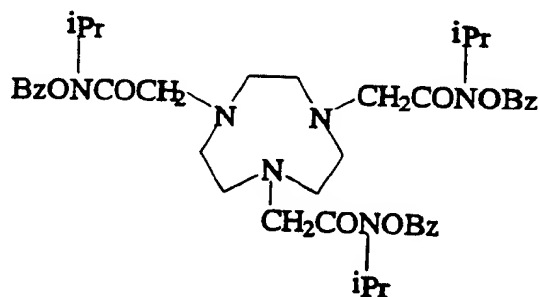
From N,N',N''-Tris[(N-methyl-N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.1) and H<sub>2</sub> and Pd/C.



1.3.5.2

**1.3.5.3      N,N',N''-Tris[(N-isopropyl-N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane trihydrobromide and chloroaceto-N-isopropyl-O-benzyl hydroxamate (1.2.7.2).

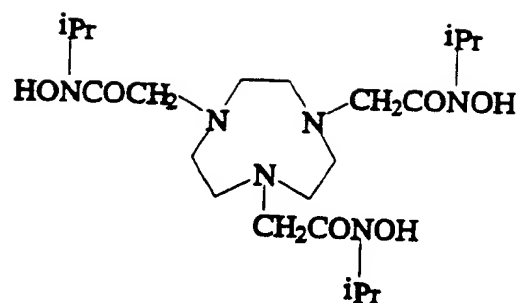


1.3.5.3

**1.3.5.4      N,N',N''-Tris[(N-isopropyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.3 and H<sub>2</sub> and Pd/C.

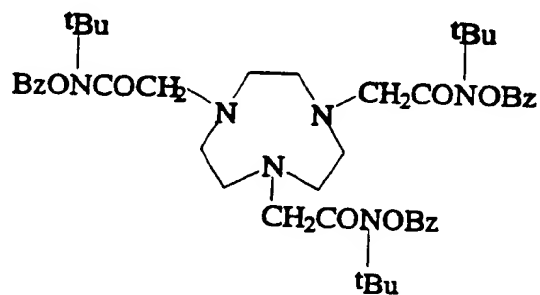
77



1.3.5.4

**1.3.5.5** **N,N',N''-Tris[(N-t-butyl-N-benzyloxycarbonylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane trihydrobromide and chloroaceto-N-t-butyl-O-benzyl hydroxamate (1.2.7.3).

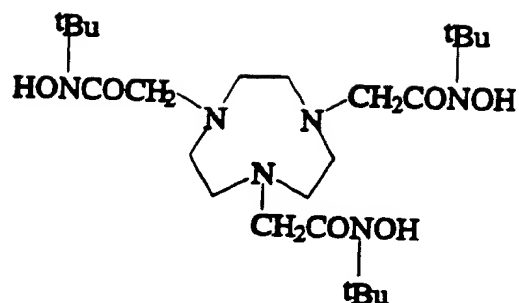


1.3.5.5

**1.3.5.6** **N,N',N''-Tris[(N-t-butyl-N-hydroxycarbonylmethyl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.5, H<sub>2</sub> and Pd/C.

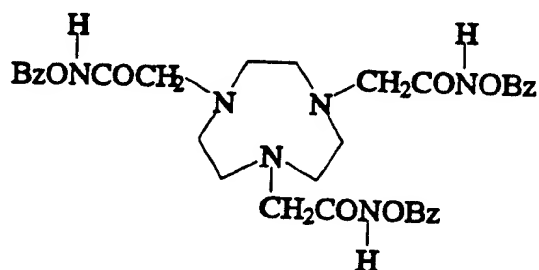
78



1.3.5.6

**1.3.5.7 N,N',N''-Tris[(N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide and chloroaceto-O-benzyl hydroxamate (1.2.7.4).

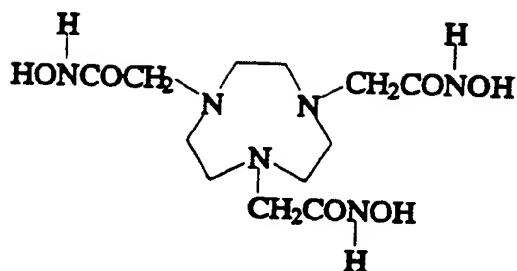


1.3.5.7

**1.3.5.8 N,N',N''-Tris[(N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.7 and H<sub>2</sub> and Pd/C.

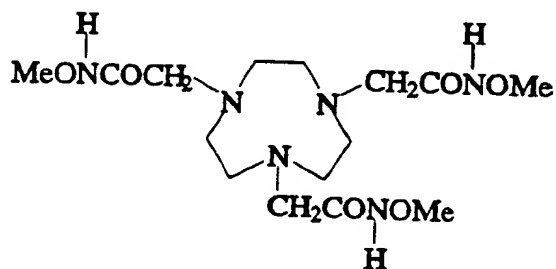
79



1.3.5.8

**1.3.5.9    N,N',N''-Tris[(N-methoxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide and chloroaceto-O-methyl hydroxamate (1.2.7.5).

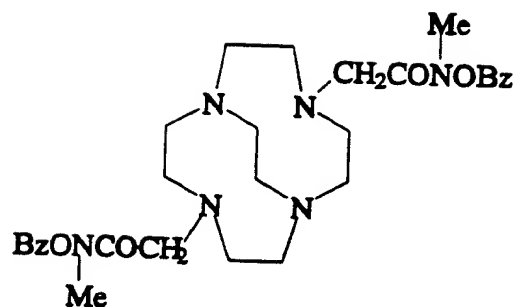


1.3.5.9

**1.3.5.10    4,10-Bis[(N-benzyloxycarbamoyl-N-methyl)methyl]-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) dihydrobromic acid, sodium carbonate and chloroaceto-O-benzyl hydroxamate (1.2.7.4).

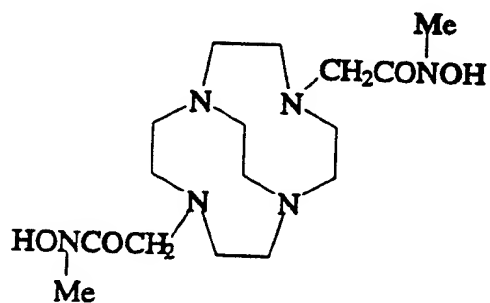
80



1.3.5.10

1.3.5.11 4,10-Bis[(N-hydroxycarbamoyl-N-methyl)methyl]-1,4,7,10-Tetraazabicyclo [5.5.2] tetradecane.

From 1.3.5.10 and  $\text{H}_2$  and Pd/C.

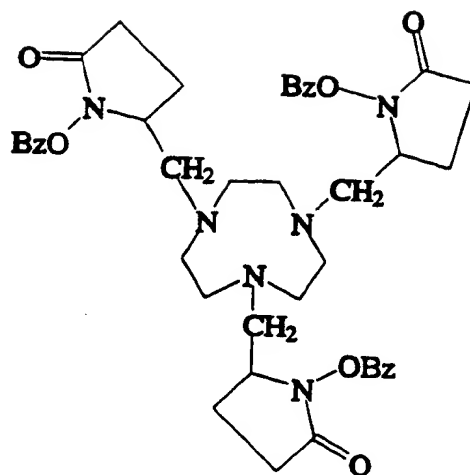


1.3.5.11

1.3.5.12 N,N',N''-Tris[(1-benzyloxy-2-pyrrolidone-5-yl)methyl]-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3), 5-(p-toluenesulfonyloxymethyl)-1-benzyloxy-2-pyrrolidone (1.2.6.3) and base.

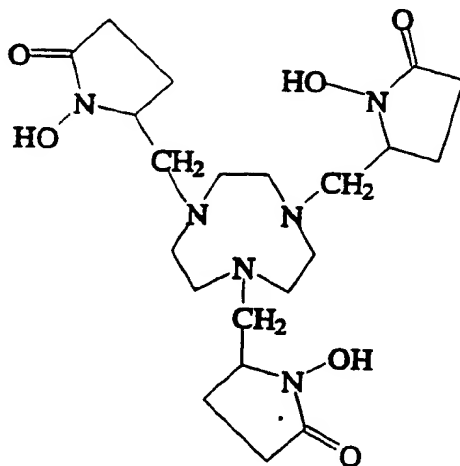
81



1.3.5.12

1.3.5.13 *N,N',N''*-Tris[(1-oxy-2-pyrrolidone-5-yl)methyl]-1,4,7-triazacyclononane.

From 1.3.5.12 and Pd/C (5%) and H<sub>2</sub>.



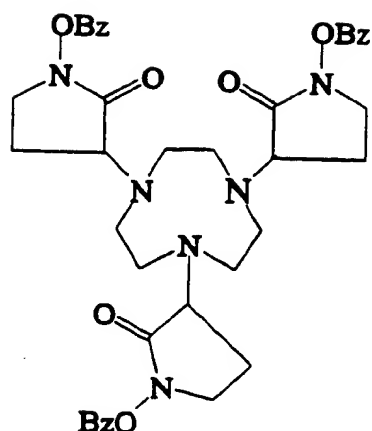
1.3.5.13

1.3.5.14 *N,N',N''*-Tris(1-benzyloxy-2-pyrrolidone-5-yl)-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3), 5-bromo-1-benzyloxy-2-pyrrolidone (1.2.6.11) and base.

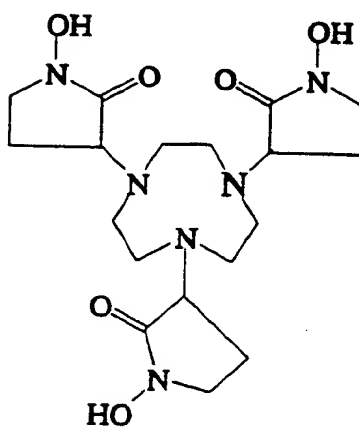
**SUBSTITUTE SHEET (RULE 26)**

82



1.3.5.14

- 1.3.5.15**     ***N,N',N''*-Tris(1-oxy-2-pyrrolidone-5-yl)-1,4,7-triazacyclononane.**  
 From 1.3.5.14 and Pd/C (5%) and H<sub>2</sub>.

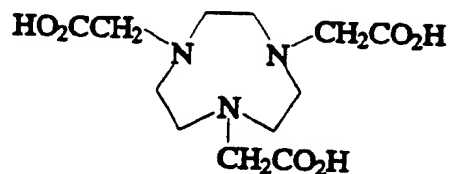


1.3.5.15

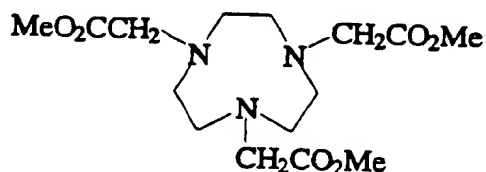
**1.3.6     Synthesis of Polyaza Ligands with Pendant Arms Containing Carboxyl Groups And The Corresponding Esters.**

Compounds were prepared by reacting polyaza bases with either halo carboxylic acids or by reductive alkylation with aldo or keto acids. The esters were prepared either by reacting directly with halo carboxylic acid esters or by reaction of the free acid with SOCl<sub>2</sub>/alcohol.

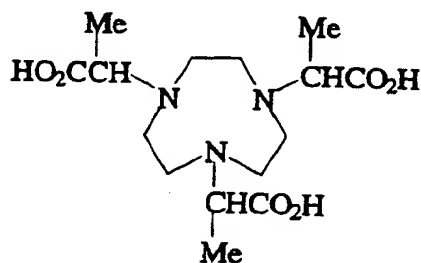
83

**1.3.6.1 N,N',N''-Tris(carboxymethyl)-1,4,7-triazacyclononane.**From 1,4,7-triazacyclononane (1.1.3), glyoxylic acid and H<sub>2</sub>/Pt.

1.3.6.1

**1.3.6.2 N,N',N''-Tris(methoxycarbonylmethyl)-1,4,7-triazacyclononane.**From N,N',N''-tris(carboxymethyl)-1,4,7-triazacyclononane in methanol and SOCl<sub>2</sub>.

1.3.6.2

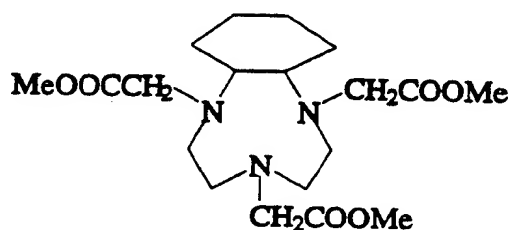
**1.3.6.3 N,N',N''-Tris(α-methylcarboxymethyl)-1,4,7-Triazacyclononane.**From 1,4,7-triazacyclononane (1.1.3), pyruvic acid and H<sub>2</sub>/Pt.

1.3.6.3

84

**1.3.6.4      N,N',N''-Tris(methoxycarbonylmethyl-1,4,7-triazabicyclo-  
[7.4.0<sup>8,13</sup>]tridecane.**

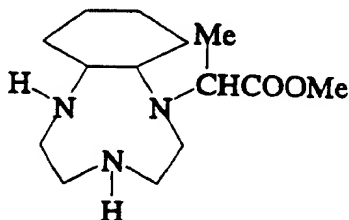
From 1,4,7-Triazabicyclo[7.4.0<sup>8,13</sup>]tridecane hydrobromide  
5 (1.1.14), glyoxylic acid and H<sub>2</sub>/PtO<sub>2</sub> in methanol.



1.3.6.4

**1.3.6.5      N-( $\alpha$ -methylcarboxymethyl)-1,4,7-triazabicyclo[7.4.0]tridecane.**

From 1,4,7-triazabicyclo[7.4.0<sup>8,13</sup>]tridecane (1.1.14), pyruvic acid  
10 and H<sub>2</sub>/PtO<sub>2</sub>.

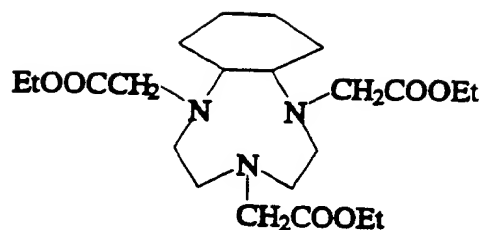


1.3.6.5

**1.3.6.6      N,N',N''-Tris(ethoxycarbonylmethyl)-1,4,7-  
triazacyclo[7.4.0]tridecane.**

15 From 1,4,7-triazabicyclo[7.4.0<sup>8,13</sup>]tridecane (1.1.14), sodium  
methoxide and ethyl bromoacetate.

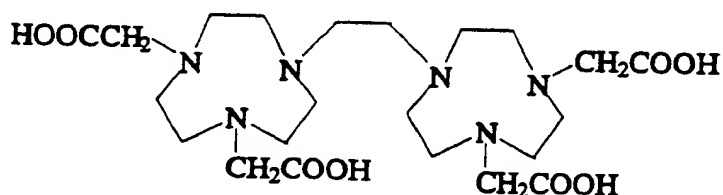
85



1.3.6.6

**1.3.6.7 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane.**

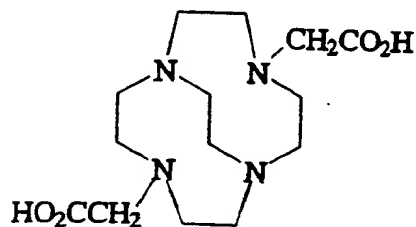
From 1,2-Bis(1,4,7-triazacyclononan-1-yl)ethane (1.1.28),  
5 chloroacetic acid and NaOH.



1.3.6.7

**1.3.6.8 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.22),  
10 chloroacetic acid and NaOH.

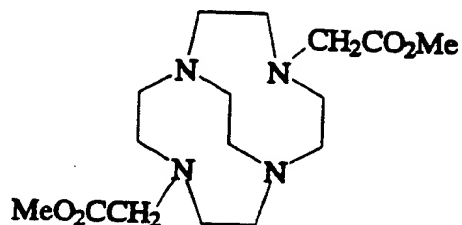


1.3.6.8

86

**1.3.6.9 4,7-Bis(methoxycarbonylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 4,7-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) in MeOH/H<sub>2</sub>SO<sub>4</sub>.

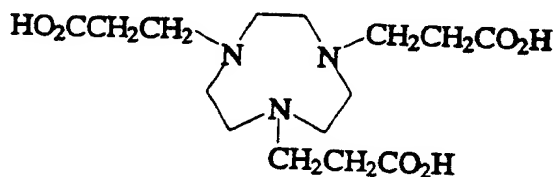


5

1.3.6.9

**1.3.6.10 N,N',N''-Tris(carboxyethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), 3-chloropropionic acid and base.



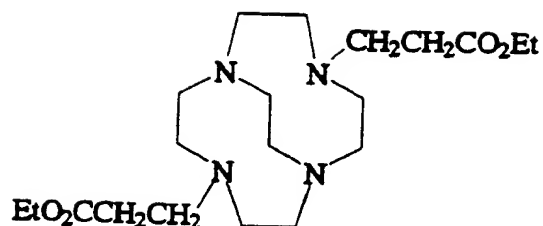
10

1.3.6.10

**1.3.6.11 4,10-Bis(ethoxycarbonylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) and ethyl acrylate.

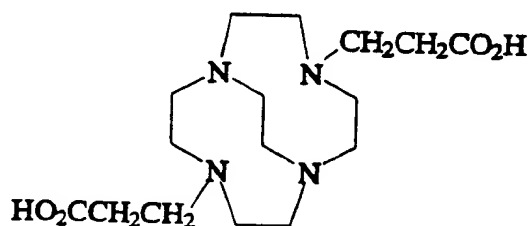
87



1.3.6.11

1.3.6.12 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.

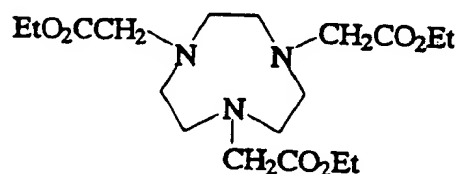
5 From 1.3.6.11 by acid hydrolysis.



1.3.6.12

1.3.6.13 N,N',N''-Tris(ethoxycarbonylmethyl)-1,4,7-triazacyclononane.

10 base. From 1,4,7-triazacyclononane (1.1.3), ethyl bromoacetate and

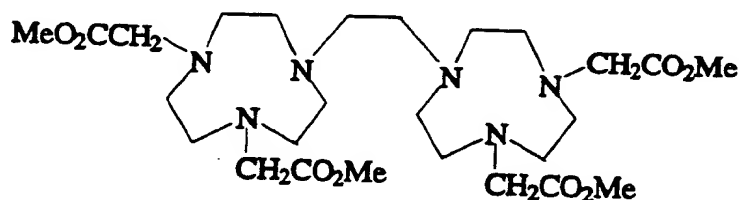


1.3.6.13

88

**1.3.6.14 1,2-Bis-(4,7-methoxycarbonylmethyl-1,4,7-triazacyclononan-1-yl)-ethane.**

From 1,2-bis-(4,7-carboxymethyl-1,4,7-Triazacyclononan-1-yl)ethane (1.3.6.7), MeOH/SOCl<sub>2</sub>.

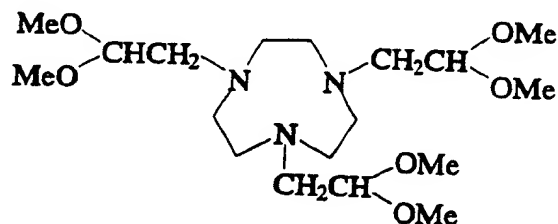


5

1.3.6.14

**1.3.7 Synthesis of Polyaza Ligands with Pendant Arms Containing Aldehyde or Ketone Groups.**

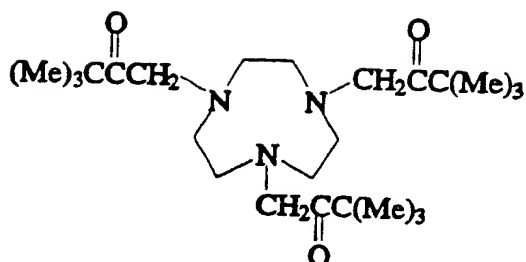
- 10 **1.3.7.1 N,N',N''-Tris(2,2-dimethoxyethyl)-1,4,7-triazacyclononane.**  
From 1,4,7-triazacyclononane (1.1.3), 1-chloro-2,2-dimethoxyethane (commercially available) and sodium carbonate.



1.3.7.1

- 15 **1.3.7.2 N,N',N''-Tris-(3,3-dimethyl-2-oxo-butyl)-1,4,7-triazacyclononane.**  
From 1,4,7-triazacyclononane (1.1.3), bromomethyl t-butyl ketone (commercially available) and sodium carbonate.

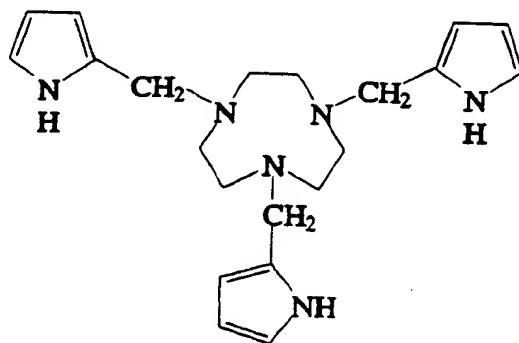
89



1.3.7.2

1.3.8 SYNTHESIS OF POLYAZA LIGANDS WITH PENDANT ARMS  
CONTAINING PYRROLE GROUPS.

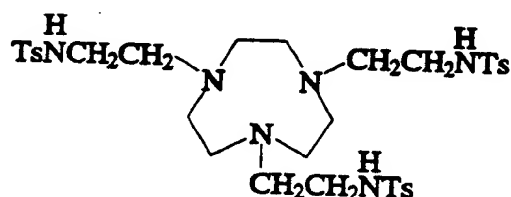
1.3.8.1 N,N',N''-Tris(-pyrrol-2-yl-methyl)-1,4,7-triazacyclononane.  
From 1,4,7-triazacyclononane (1.1.3), pyrrole-2-carboxaldehyde  
(commercially available) and H<sub>2</sub>/PtO<sub>2</sub>.



1.3.8.1

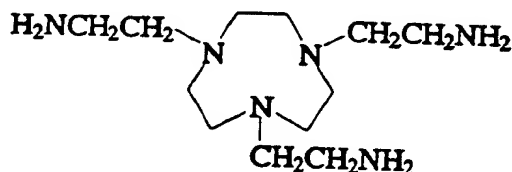
**1.3.9 SYNTHESIS OF POLYAZA LIGANDS WITH PENDANT ARMS CONTAINING AMINE GROUPS.**

- 5 **1.3.9.1** **N,N',N''-Tris(2-p-toluenesulfonyloxyethyl)-1,4,7-triazacyclononane.**  
From 1,4,7-triazacyclononane (1.1.3), 2-(p-toluenesulfonylamino)-1-(p-toluenesulfonyloxy)ethane (1.1.16) and base.



**1.3.9.1**

- 10 **1.3.9.2** **N,N',N''-Tris(2-aminoethyl)-1,4,7-triazacyclononane.**  
From 1.3.9.1 and HBr/acetic acid.



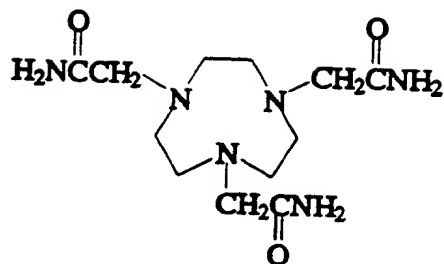
**1.3.9.2**

- 15 **1.3.10 Synthesis of Polyaza Ligands with Pendant Arms Containing Amide Groups.**

**1.3.10.1 N,N',N''-Tris(methylcarboxamide)-1,4,7-triazacyclononane.**

- From N,N',N''-Tris-(methoxycarbonylmethyl)-1,4,7-triazacyclononane (1.3.6.2) and ammonia.
- 20

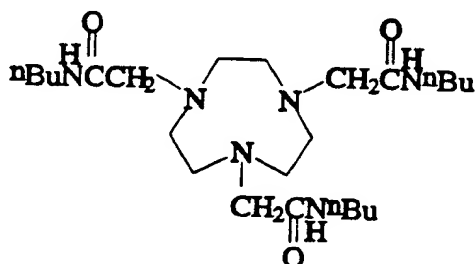
91



1.3.10.1

**1.3.10.2** **N,N',N''-Tris[-N-n-butyl(methylcarboxamide)]-1,4,7-triazacyclononane.**

From N,N',N''-Tris-(methoxycarbonylmethyl)-1,4,7-triazacyclononane (1.3.6.2) and butylamine.

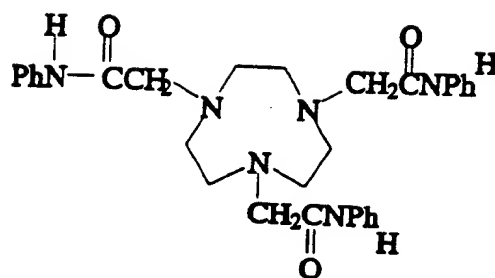


1.3.10.2

**1.3.10.3** **N,N',N''-Tris[-N-n-phenyl(methylcarboxamide)]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), N-phenylchloroacetamide (prepared from aniline and chloroacetyl chloride) and excess sodium carbonate.

92



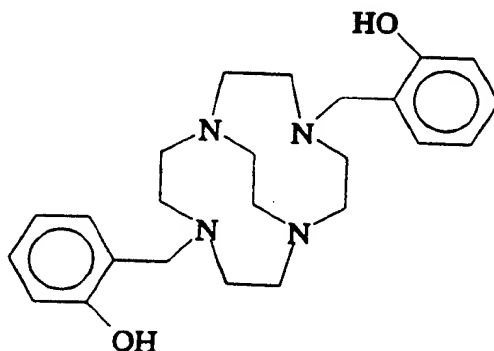
1.3.10.3

**1.3.11 Synthesis of Polyaza Ligands with Pendant Arms Containing Phenolic Groups.**

5

**1.3.11.1 4,7-Di-(2-hydroxy-benzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20),  
 10 salicylaldehyde (excess) and  $H_2/PtO_2$ .

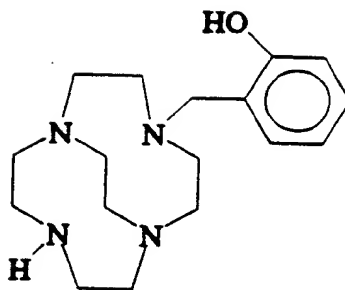


1.3.11.1

**1.3.11.2 4-(2-hydroxy-benzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20),  
 15 salicylaldehyde (1.5 equivalents) and  $H_2/PtO_2$ .

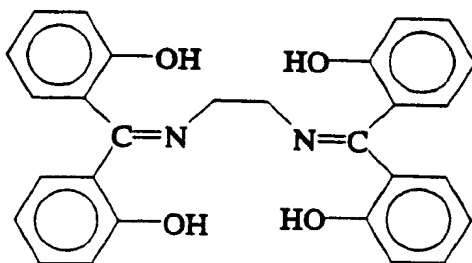
93



1.3.11.2

**1.3.11.3 Bis-(2,2'-dihydroxybiphenylmethylene) ethylene diamine.**

From ethylenediamine (1.1.0) and 2,2'-dihydroxy benzophenone  
 5 (commercially available) with removal of H<sub>2</sub>O.

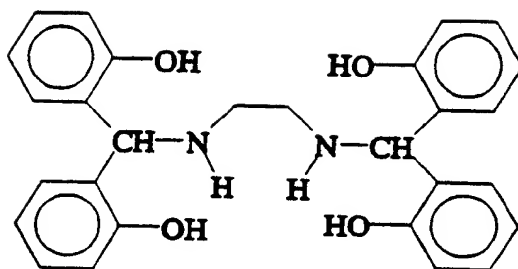


1.3.11.3

**1.3.11.4 N,N'-Bis-(2,2'-dihydroxybiphenylmethyl) ethylene diamine.**

From 1.3.11.3 and sodium borohydride.

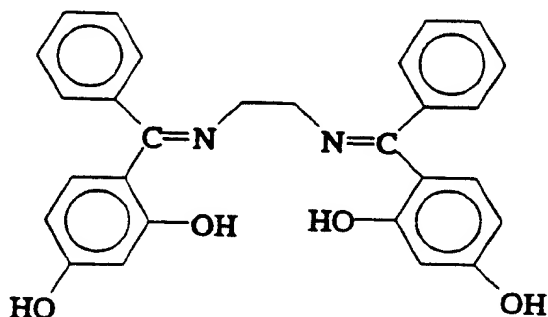
94



1.3.11.4

**1.3.11.5 Bis-(2,4-dihydroxybiphenylmethylene) ethylenediamine.**

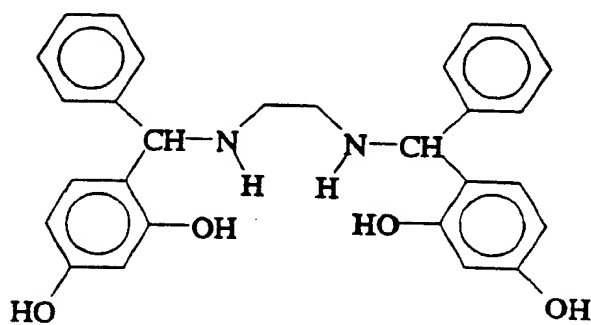
From ethylenediamine (1.1.0) and 2,4-dihydroxy benzophenone  
5 (commercially available) with removal of H<sub>2</sub>O.



1.3.11.5

**1.3.11.6 N,N'-Bis-(2,4-dihydroxybiphenylmethyl) ethylenediamine.**

From 1.3.11.5 and sodium borohydride.

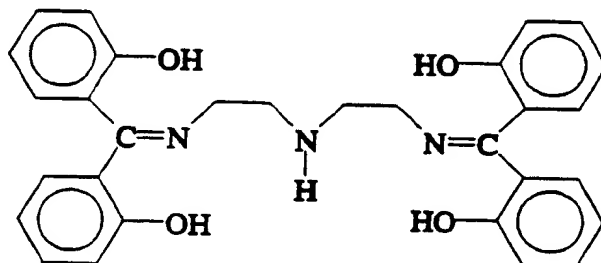


1.3.11.6

95

**1.3.11.7 N,N''-Bis-(2,2'-dihydroxybiphenylmethylen) diethylene triamine.**

From diethylene triamine (1.1.1) and 2,2'-dihydroxy benzophenone with removal of H<sub>2</sub>O.

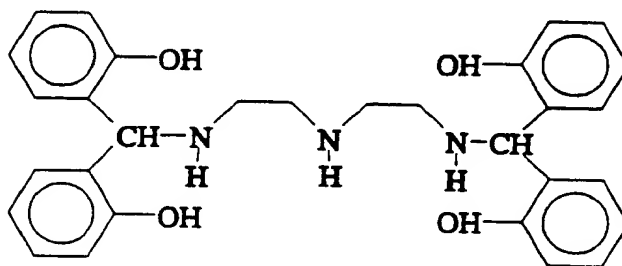


1.3.11.7

5

**1.3.11.8 N,N''-Bis-(2,2'-dihydroxybiphenylmethyl) diethylene triamine.**

From 1.3.11.7 and sodium borohydride.

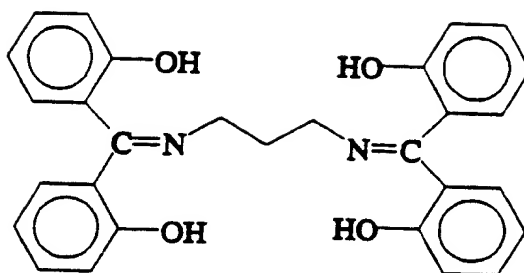


1.3.11.8

**1.3.11.9 Bis-(2,2'-dihydroxybiphenylmethylen)-1,3-diaminopropane.**

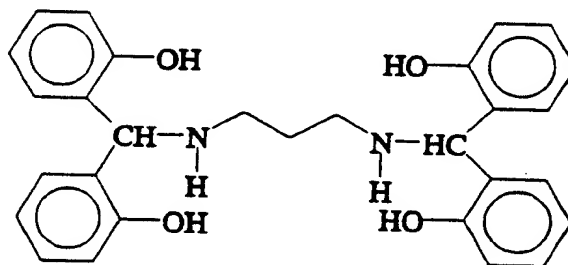
From diaminopropane and 2,2'-dihydroxy benzophenone with removal of H<sub>2</sub>O.

96



1.3.11.9

- 1.3.11.10** **N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)-1,3-diaminopropane.**  
From and 1.3.11.9 and sodium borohydride.

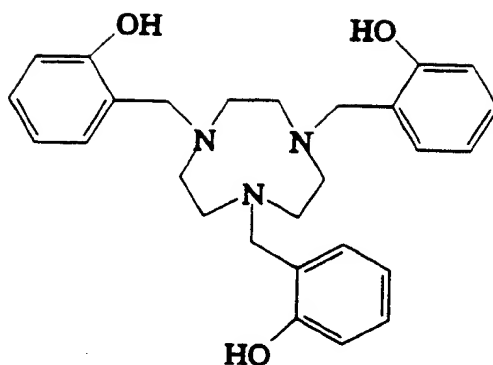


1.3.11.10

5

- 1.3.11.11** **N,N',N''-Tris(2-hydroxybenzyl)-1,4,7-triazacyclononane.**  
From 1,4,7-triazacyclononane, salicylaldehyde and  $H_2/PtO_2$ .

97



1.3.11.11

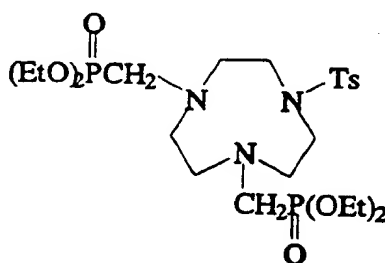
**1.3.12 Synthesis of Polyaza Ligands with More Than One Species of Pendant Arm.**

5

**1.3.12.1 N-(p-Toluenesulfonyl)-N', N''-bis(diethylphosphorylmethyl)-1,4,7-triazacyclononane.**

From N-(p-toluenesulfonyl)-1,4,7-triazacyclononane dihydrobromide

10 (1.3.13.31), formaldehyde and diethyl phosphite.



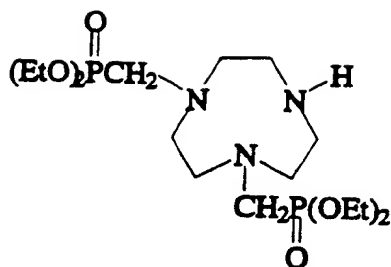
1.3.12.1

**1.3.12.2 N,N'-Bis(diethylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, one

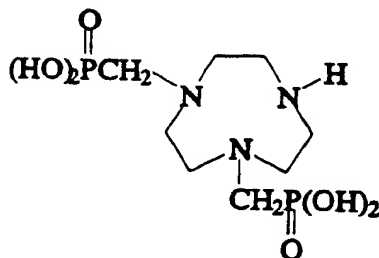
15 equivalent formaldehyde and one equivalent of diethyl phosphite. Purification of product by chromatography.

98.



1.3.12.2

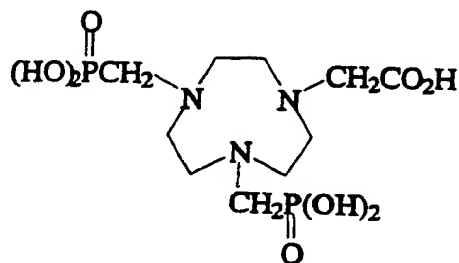
- 1.3.12.3** **N,N'-Bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane.**  
From 1.3.12.2 and HCl.



1.3.12.3

5

- 1.3.12.4** **N-(Carboxymethyl)-N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane.**  
From 1.3.12.3, chloroacetic and NaOH.



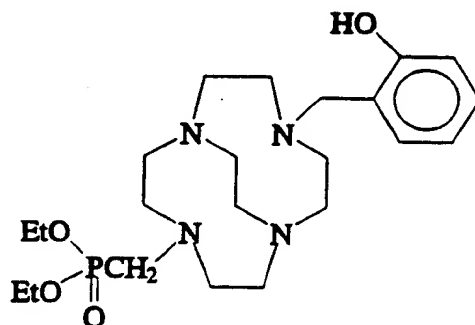
1.3.12.4

10

99

**1.3.12.5 4-(2-Hydroxy-benzyl)-7-diethylphosphorylethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 4-(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.2), diethyl phosphite and  
5 formaldehyde solution.

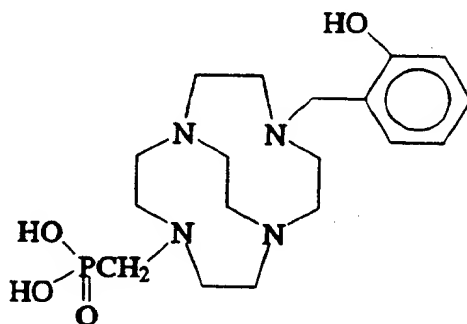


1.3.12.5

**1.3.12.6 4-(2-hydroxy-benzyl)-7-phosphorylethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

10

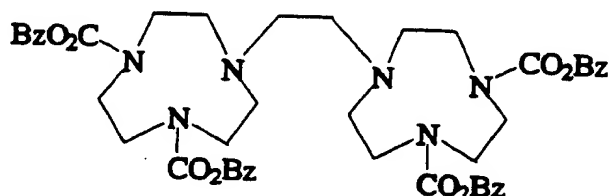
From 1.3.12.5 and HCl.



1.3.12.6

**1.3.13 Miscellaneous Substituted Polyaza Compounds.****1.3.13.1 1,2-Bis-(4,7-benzyloxycarbonyl-1,4,7-triazacyclononan-1-yl)ethane.**

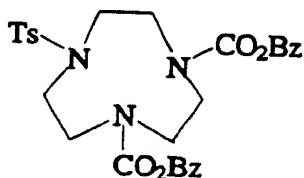
From 1,2-bis-(1,4,7-triazacyclononan-1-yl)ethane(1.1.28)  
polyhydrobromide, potassium carbonate and benzyl chloroformate.



5

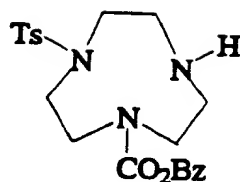
**1.3.13.1****1.3.13.2 N-(p-Toluenesulfonyl)-N',N''-Bis-(benzyloxycarbonyl)-1,4,7-triazacyclononane.**

From N-(p-toluenesulfonyl)-1,4,7-triazacyclononane dihydrobromide  
10 (1.3.13.31),  $K_2CO_3$  and benzyl chloroformate.

**1.3.13.2****1.3.13.3 N-(p-Toluenesulfonyl)-N''-benzyloxycarbonyl-1,4,7-triazacyclononane.**

15 From N-(p-toluenesulfonyl)-N',N''-bis(benzyloxycarbonyl)-1,4,7-triazacyclononane (1.3.13.2) and trimethylsilyl iodide.

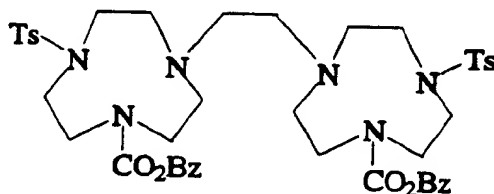
101



1.3.13.3

**1.3.13.4 1,2-Bis[(1-p-toluenesulfonyl)-4-benzyloxycarbonyl-1,4,7-triazacyclonon-7-yl]ethane.**

5 From 1-(p-toluenesulfonyl)-4-benzyloxycarbonyl-1,4,7-triazacyclononane (1.3.13.3), potassium carbonate and dibromoethane.

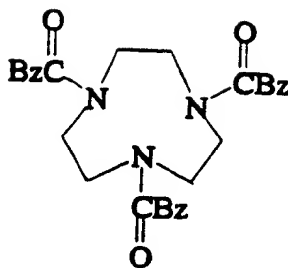


1.3.13.4

**1.3.13.5 N,N',N''-Tris(phenylacetyl)-1,4,7-triazacyclononane.**

10 From 1,4,7-triazacyclononane (1.1.3), diethyl phenylacetylphosphonate [PhCH<sub>2</sub>COP(O)(OEt)<sub>2</sub>].

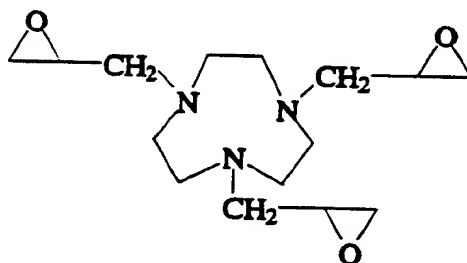
102



1.3.13.5

**1.3.13.6 N,N',N''-Tris(2,3-Epoxypropyl)-1,4,7-Triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and epibromohydrin.

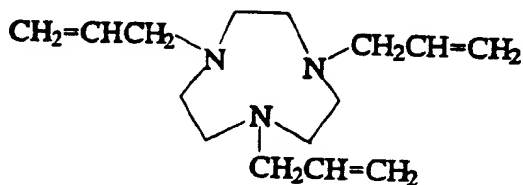


1.3.13.6

5

**1.3.13.7 N,N',N''-Tri-allyl-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), sodium hydride and allyl bromide.



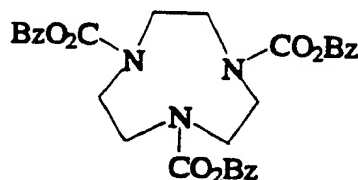
1.3.13.7

10

103

**1.3.13.8 N,N',N''-Tris(benzyloxycarbonyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), benzyl chloroformate and sodium carbonate.

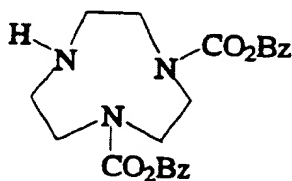


1.3.13.8

5

**1.3.13.9 N,N'-Bis(benzyloxycarbonyl)-1,4,7-triazacyclononane.**

From N,N',N''-tris(benzyloxycarbonyl)-1,4,7-triazacyclononane (1.3.13.8) and iodotrimethylsilane.



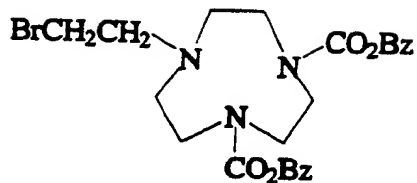
1.3.13.9

10

**1.3.13.10 N,N'-Bis(benzyloxycarbonyl)-N''-(2-bromoethyl)-1,4,7-triazacyclononane.**

From N,N'-bis(benzyloxycarbonyl)-1,4,7-triazacyclononane (1.3.13.9), dibromoethane and potassium carbonate.

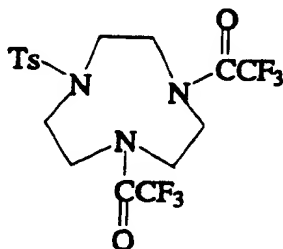
104



1.3.13.10

**1.3.13.11 N-p-Toluenesulfonyl-N',N"-ditrifluoroacetyl-1,4,7-triazacyclononane.**

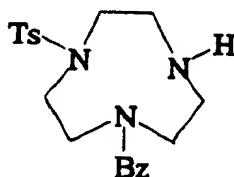
5 From N-p-toluenesulfonyl-1,4,7-triazacyclononane (1.3.13.31), potassium carbonate and trifluoroacetic anhydride.



1.3.13.11

**1.3.13.12 N-p-Toluenesulfonyl-N'-benzyl-1,4,7-triazacyclononane.**

10 From N-(p-toluenesulfonyl-1,4,7-triazacyclononane (1.3.13.31), sodium hydride and benzyl bromide.

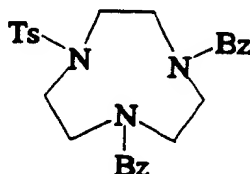


1.3.13.12

105

**1.3.13.13 N-p-Toluenesulfonyl-N',N"-dibenzyl-1,4,7-triazacyclononane.**

From N-(p-toluenesulfonyl-1,4,7-triazacyclononane (1.3.13.31), sodium hydride and benzyl bromide.

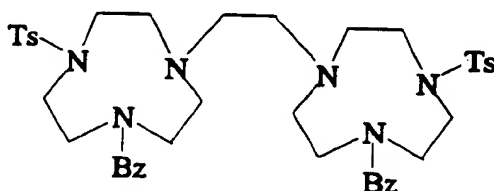


1.3.13.13

5

**1.3.13.14 1,2-Bis(N-p-toluenesulfonyl-N'-benzyl)-1,4,7-triazacyclononan-1-yl) ethane.**

From N-p-toluenesulfonyl-N'-benzyl-1,4,7-triazacyclononane (1.3.13.12), dibromoethane and potassium carbonate.



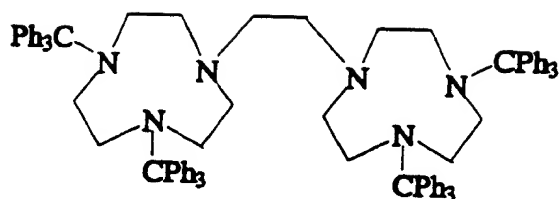
1.3.13.14

10

**1.3.13.15 1,2-Bis(N,N'-ditrityl-1,4,7-triazacyclononan-1-yl)ethane.**

From 1,2-Bis(1,4,7-triazacyclononane)ethane (1.1.28), potassium carbonate and trityl chloride.

106

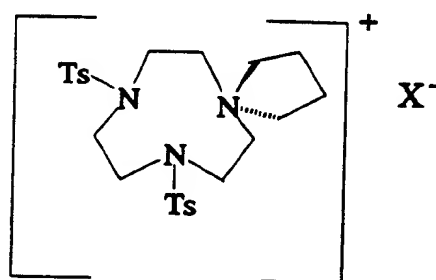


1.3.13.15

**1.3.13.16 Spiro [4,8]-4,7-di-p-toluenesulfonyl-4,7-diaza-1-azotridecane halide.**

From 1,4,7-triazacyclononane-N,N'-di-p-toluenesulfonyl

5 hydrobromide (1.3.13.32), diiodobutane and potassium carbonate.

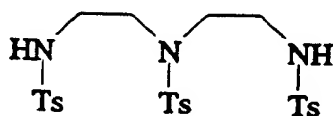


1.3.13.16

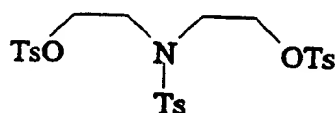
**1.3.13.17 Tetrakis(p-toluenesulfonyl)-1,4,7,10-tetraazacyclotetradecane.**

From N,N',N''-tris(p-toluenesulfonyl)diethylenetriamine (1.3.13.18),

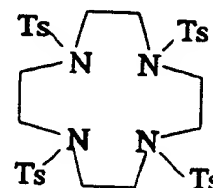
10 potassium carbonate and bis(2-p-toluenesulfonyloxyethyl)-N-(p-toluenesulfonyl) amine (1.3.13.19).



1.3.13.18



1.3.13.19

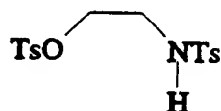


1.3.13.17

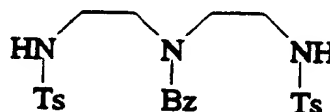
107

**1.3.13.20 1,7-Bis(p-toluenesulfonyl)-4-benzyl-1,4,7-triazaheptane.**

From benzylamine, (2-p-toluenesulfonyloxy)-N-(p-toluenesulfonyl)-ethylamine (1.3.13.21) and potassium carbonate.



1.3.13.21

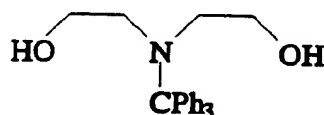


1.3.13.20

5

**1.3.13.22 N-Trityldiethanolamine.**

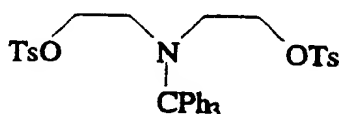
From diethanolamine and trityl chloride.



1.3.13.22

**1.3.13.23 N-Trityl-bis(2-p-toluenesulfonyloxyethyl)amine.**

From N-trityldiethanolamine and p-toluenesulfonyl chloride.

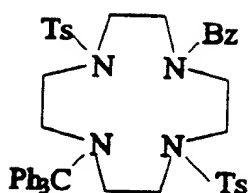


1.3.13.23

**1.3.13.24 1,7-di-(p-toluenesulfonyl)-4-benzyl-10-trityl-1,4,7,10-tetraazacyclotetradecane.**

From 1,7-di-p-toluenesulfonyl-4-benzyl-1,4,7-triazaheptane (1.3.13.20), sodium hydride and N-trityl-di-p-toluenesulfonyldiethanolamine (1.3.13.23).

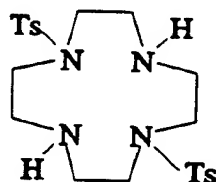
108



1.3.13.24

**1.3.13.25** 1,7-Di-(p-toluenesulfonyl)-1,4,7,10-tetraazacyclotetradecane.

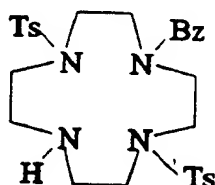
From 1,7-di-(p-toluenesulfonyl)-4-benzyl-10-trityl-1,4,7,10-tetraazacyclotetradecane (1.3.13.24) reduced by H<sub>2</sub> and Pd/C.



1.3.13.25

**1.3.13.26** 1,7-Di-(p-toluenesulfonyl)-4-benzyl-1,4,7,10-tetraazacyclotetradecane.

From reduction of 1.3.13.24.

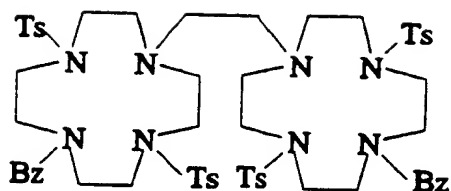


1.3.13.26

**1.3.13.27** 1,2-Bis-(4,10-di-p-toluenesulfonyl-7-benzyl-1,4,7,10-tetraazacyclotetradecan-1-yl)ethane.

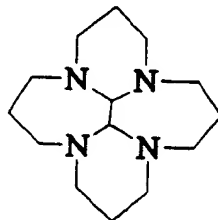
From 1.3.13.26 and dibromoethane.

109



1.3.13.27

**1.3.13.28** 1,5,9,13-Tetraazatetracyclo[6,6,2,0<sup>1,15</sup>, 0<sup>8,16</sup>]hexadecane  
From 1.1.6 and glyoxaldehyde.

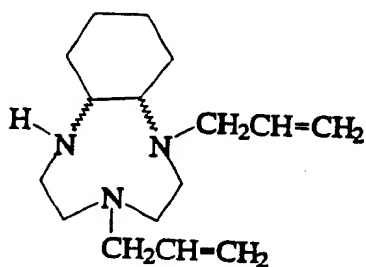


1.3.13.28

5

**1.3.13.29** 4,7-Diallyl-1,4,7-triazabicyclo[7,4,0]tridecane.

From 1,4,7-triazabicyclo[7,4,0]tridecane trihydrobromide (1.1.14), sodium hydride and allyl bromide.



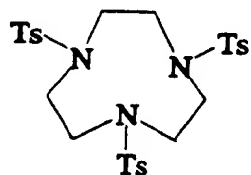
1.3.13.29

10

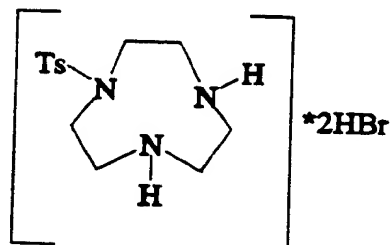
110

**1.3.13.30 N-p-Toluenesulfonyl-1,4,7-triazacyclononane dihydrobromide.**

From N,N',N''-Tris(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.3.13.31) prepared from 1.3.13.18, dibromoethane and base) and HBr/acetic acid.



1.3.13.31

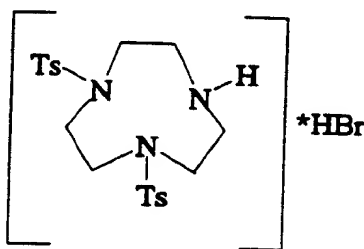


1.3.13.30

5

**1.3.13.32 N,N'-Di-p-Toluenesulfonyl-1,4,7-triazacyclononane hydrobromide.**

a) From N,N',N''-tris(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.3.13.31) and HBr/acetic acid as the hydrobromide salt.

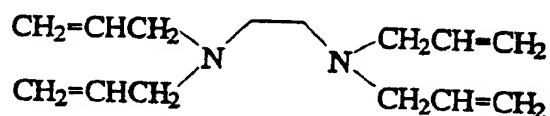


1.3.13.32

10

**1.3.13.33 N,N,N',N'-Tetraallylethylenediamine.**

From ethylenediamine, sodium carbonate and allyl bromide.



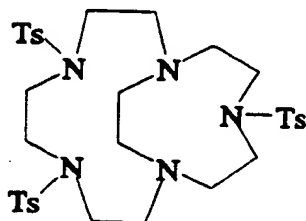
1.3.13.33

15

111

**1.3.13.34 4,7,13-Tris(p-toluenesulfonyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane.**

From 1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.1.26), potassium carbonate and p-toluenesulfonyl chloride.

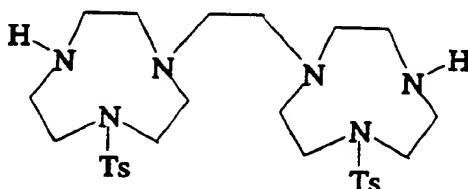


1.3.13.34

5

**1.3.13.35 1,2-Bis(4-p-toluenesulfonyl-1,4,7-triazacyclonon-1-yl)ethane.**

From 1,2-bis(4,7-di-p-toluenesulfonyl-1,4,7-triazacyclonon-1-yl)ethane (1.1.30) and sulphuric acid.



1.3.13.35

10

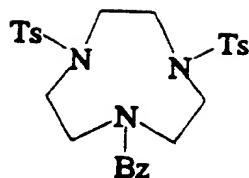
**1.3.13.36 N,N'-(Di-p-toluenesulfonyl)-N''-benzyl-1,4,7-Triazacyclononane.**

a) From N,N''-(p-toluenesulfonyl)-4-benzyl diethylenetriamine (1.3.13.20), sodium hydride and ethylene glycol di-p-toluenesulfonate (1.1.12).

b) From N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.3.13.32), sodium hydride and benzyl bromide.

15

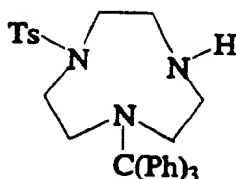
112



1.3.13.36

**1.3.13.37 N-(p-Toluenesulfonyl)-N'-trityl-1,4,7-triazacyclononane.**

From N-(p-toluenesulfonyl-1,4,7-triazacyclononane dihydrobromide  
5 (1.3.13.30), sodium hydride and trityl chloride.



1.3.13.37

**1.3.13.38 Hexakis(allyl) triethylenetetramine.**

From triethylenetetramine (1.1.2), sodium carbonate and allyl  
10 bromide.

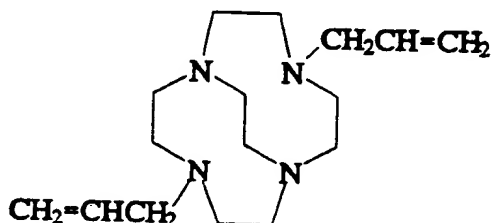


1.3.13.38

113

**1.3.13.39 4,7-diallyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.4), allyl bromide and base.



1.3.13.39

5

**EXAMPLE 2**

This example illustrates the preparation of metal complexes using the chelating agents (ligands) described in Example 1.

10

**2.1 Synthesis of Metal Complexes**

Water soluble salts of metals and compounds described in the above examples were heated in water or alcohol solvents followed by base addition to neutral or basic pH. Alternately, an excess of these metals in the form of their corresponding insoluble oxides or hydroxides was heated with the acid form of the compounds described in preceding sections until complexation was complete, followed by filtration to remove uncomplexed excess metal oxide or hydroxide. In either case complex formation was verified by chromatography. Employing these methods the following complexes were synthesized:

20

2.1.1 Iron (III) complexes with the following Compounds:

2.1.1.1. 1,2-Bis(1,4,7-triazabicyclononan-1-yl)ethane (1.1.29)

2.1.1.2. N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.1)

5 2.1.1.3. (R, R, R) N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.2).

2.1.1.4. (S, S, S) N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.3).

10 2.1.1.5. N,N',N"-Tris(2-hydroxy-3-isobutoxypropyl)-1,4,7-triazacyclononane (1.3.1.4).

2.1.1.6. (R, R, R) N,N',N"-Tris(2-hydroxy-3-isobutoxypropyl)-1,4,7-triazacyclononane (1.3.1.5).

2.1.1.7. N,N',N"-Tris(2-hydroxy-3-methoxypropyl)-1,4,7-triazacyclononane (1.3.1.6).

15 2.1.1.8. N,N',N"-Tris(2,3-dihydroxypropyl)-1,4,7-triazacyclononane (1.3.1.7).

2.1.1.9. N,N',N"-Tris(2-hydroxy-3-allyloxypropyl)-1,4,7-triazacyclononane (1.3.1.9).

20 2.1.1.10. N,N',N"-Tris(2-hydroxy-3-phenoxypropyl)-1,4,7-triazacyclononane (1.3.1.10 ).

2.1.1.11. N,N',N"-Tris(2-hydroxy-2,2-diethoxymethylene)ethyl-1,4,7-triazacyclononane (1.3.1.11).

2.1.1.12. N,N',N"-Tris(2-hydroxy-2,2-dimethoxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.12).

25 2.1.1.13. N,N',N"-Tris(2-hydroxy-2,2-diisopropyloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).

2.1.1.14. N,N',N"-Tris[2-hydroxy-bis(2-furfurylmethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.14).

30 2.1.1.15. N,N',N"-Tris(3-hydroxy-1,5-dioxacycloheptyl-3-methyl)-1,4,7-triazacyclononane (1.3.1.15 ).

2.1.1.16. N,N',N"-Tris[(3-Hydroxy-7,7-dimethyl-1,5-dioxacyclooct-3-yl)-methyl]-1,4,7-triazacyclononane (1.3.1.16).

- 2.1.1.17. N,N',N"-Tris[(3-hydroxy-7-methyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.17).
- 2.1.1.18. N,N',N"-Tris[(3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-Triazacyclononane (1.3.1.18).
- 5 2.1.1.19. N,N',N"-Tris[(3-hydroxy-benzo[b]-1,5-dioxacycloheptyl)methyl]1,4,7-triazacyclononane (1.3.1.19).
- 2.1.1.20. N,N',N"-Tris[(3-hydroxy-1,5-dioxacyclooctan-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.20).
- 2.1.1.21. N,N',N"-Tris[(4-fluoro-2-hydroxy-3-isopropyl-4-methyl)pentyl]-1,4,7- triazacyclononane (1.3.1.22).
- 10 2.1.1.22. N,N',N"-Tris-[2-hydroxy-3-(1-fluoroethyl)-4-hydroxypentyl]-1,4,7-triazacyclononane (1.3.1.23).
- 2.1.1.23. N,N',N"-Tris[2-hydroxy-2-(1-fluoroethyl)-2-(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.24).
- 15 2.1.1.24. N,N',N"-Tris(2-hydroxy-2-ethyl-3-methoxybutyl)-1,4,7-triazacyclononane (1.3.1.25).
- 2.1.1.25. N,N',N"-Tris[(2,3-dihydroxy-2-ethyl)butyl]-1,4,7-triazacyclononane (1.3.1.26).
- 2.1.1.26. N,N',N"-Tris[2-hydroxy-2,2-bis(1-fluoroethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.27).
- 20 2.1.1.27. N,N',N"-Tris[2-hydroxy-2,2-bis(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.28).
- 2.1.1.28. N,N',N"-Tris[(3,3-dimethyl-2-hydroxy)butyl]-1,4,7-triazacyclononane (1.3.1.29).
- 25 2.1.1.29. N,N',N"-Tris(2-hydroxycyclohexan-1-yl)-1,4,7-triazacyclononane (1.3.1.33).
- 2.1.1.30. N,N',N",N"'-Tetrakis(2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclotetradecane (1.3.1.38).
- 2.1.1.31. 4,10-Bis(2-hydroxypropyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.1.39).
- 30 2.1.1.32. 4,10-Bis-(2-hydroxyethyl)-1,4,7,10-tetrazabicyclo[5.5.2]tetradecane (1.3.1.40).

- 2.1.1.33. 4,10-Bis-(2,3-dihydroxypropyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.1.42).
- 2.1.1.34. N,N',N"-Tris[(2,4-dihydroxy-3-isopropyl-4-methyl)pentyl]-1,4,7-triazacyclononane (1.3.1.54).
- 5 2.1.1.35. N,N',N"-Tris(2-hydroxy-bis(2,2-dihydroxymethyl)ethyl)-1,4,7-triazacyclononane (1.3.1.55).
- 2.1.1.36. N,N',N"-Tris(dihydroxyphosphoryl mono butyl ester)methyl-1,4,7-triazacyclononane (1.3.2.2).
- 2.1.1.37. N,N',N"-Tris(dihydroxyphosphorylmethyl monoethyl ester)-  
10 1,4,7-triazacyclononane (1.3.2.4).
- 2.1.1.38. N,N',N"-Tris(dihydroxyphosphorylmethyl monoethyl ester)-1,4,7-triazacyclononane (1.3.2.6).
- 2.1.1.39. N,N',N"-Tris(dihydroxyphosphorylmethyl monoisobutyl ester)-1,4,7-triazacyclononane (1.3.2.8).
- 15 2.1.1.40. 1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)ethane (1.3.3.1).
- 2.1.1.41. 1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)propane (1.3.3.2).
- 2.1.1.42. 4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane.  
20
- 2.1.1.43. 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.3.4).
- 2.1.1.44. N,N',N"-Tris(dihydroxyphosphorylethyl)-1,4,7-triazacyclononane (1.3.3.5).
- 25 2.1.1.45. N',N'',N''',N''''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane (1.3.3.6).
- 2.1.1.46. 4,10-Bis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.3.7).
- 2.1.1.47. N,N',N"-Tris[(N-methyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.2).  
30
- 2.1.1.48. N,N',N"-Tris[(N-isopropyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.4).

- 2.1.1.49. **N,N',N''-Tris[(N-t-butyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.6).**
- 2.1.1.50. **N,N',N''-Tris[(N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.8).**
- 5 2.1.1.51. **N,N',N''-Tris[(N-methoxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.9).**
- 2.1.1.52. **4,10-Bis[(N-hydroxy-N-methylcarbamoyl)methyl]-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.5.11).**
- 10 2.1.1.53. **N,N',N''-Tris[(1-hydroxy-2-pyrrolidon-5-yl)methyl]-1,4,7-triazacyclononane (1.3.5.13).**
- 2.1.1.54. **N,N',N''-Tris[(1-hydroxy-2-pyrrolidon-5-yl)methyl]-1,4,7-triazacyclononane (1.3.5.13).**
- 2.1.1.55. **N,N',N''-Tris(carboxymethyl)-1,4,7-triazacyclononane (1.3.6.1).**
- 2.1.1.56. **1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).**
- 15 2.1.1.57. **N,N',N''-Tris(carboxyethyl)-1,4,7-triazacyclononane (1.3.6.10).**
- 2.1.1.58. **4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).**
- 2.1.1.59. **N,N',N''-Tris(2,2-dimethoxyethyl)-1,4,7-triazacyclononane (1.3.7.1).**
- 20 2.1.1.60. **N,N',N''-Tris(pyrrol-2-yl-methyl)-1,4,7-triazacyclononane (1.3.8.1).**
- 2.1.1.61. **N,N',N''-Tris[N-n-butyl(carbamoylmethyl)]-1,4,7-triazacyclononane (1.3.10.2).**
- 2.1.1.62. **N,N',N''-Tris[N-phenyl(carbamoylmethyl)]-1,4,7-triazacyclononane (1.3.10.3).**
- 25 2.1.1.63. **4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).**
- 2.1.1.64. **N,N'-Bis-(2,4-dihydroxybiphenylmethyl)ethylenediamine (1.3.11.6).**
- 2.1.1.65. **N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)diethylenetriamine (1.3.11.8).**
- 30 2.1.1.66. **N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)-1,3-diaminopropane (1.3.11.10).**

- 2.1.1.67. **N,N',N''-Tris(2-hydroxybenzyl)-1,4,7-triazacyclononane (1.3.11.11).**
- 2.1.1.68. **N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-Triazacyclononane (1.3.12.3).**
- 5 2.1.1.69. **N-(carboxymethyl)-N',N''-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (1.3.12.4).**

**2.1.2 Gadolinium (III) complexes with the following chelators:**

- 10 2.1.2.1. **1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)ethane (1.3.1.13).**
- 2.1.2.2. **1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)propane (1.3.3.2).**
- 2.1.2.3. **4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-**  
15 **pentaazabicyclo[8.5.2]heptadecane (1.3.3.4).**
- 2.1.2.4. **N,N',N'', N'''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane (1.3.3.6).**
- 2.1.2.5. **N,N',N''-Tris[2-dihydroxyphosphoryl-1-hydroxy]ethyl-1,4,7-triazacyclononane (1.3.4.3).**
- 20 2.1.2.6. **1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).**
- 2.1.2.7. **N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)ethylenediamine (1.3.11.4).**
- 2.1.2.8. **N,N'-Bis-(2,4-dihydroxybiphenylmethyl)ethylenediamine (1.3.11.6).**

**2.1.3 Copper (II) complexes with the following Compounds:**

- 2.1.3.1. **1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (1.1.22).**
- 2.1.3.2. **N,N',N''-Tris(2-hydroxy-2,2-diisopropoxyethyl)-1,4,7-**  
30 **triazacyclononane (1.3.1.13).**
- 2.1.3.3. **4,10-Bis(2-Hydroxypropyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.1.39).**

- 2.1.3.4. 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).
- 2.1.3.5. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).
- 5 2.1.3.6. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.1.4 Zinc (II) complexes with the following Compounds:
- 10 2.1.4.1. N,N',N"-Tris(2-hydroxy-2,2-diisopropoxyloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).
- 2.1.4.2. 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).
- 2.1.4.3. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).
- 15 2.1.4.4. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.1.5 Manganese (II) complexes with the following Compounds:
- 20 2.1.5.1. 4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.3.3).
- 2.1.5.2. 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo [8.5.2]heptadecane (1.3.3.4).
- 25 2.1.5.3. 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).
- 2.1.5.4. 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).

2.1.6 Cadmium (II) complexes with the following Compounds:

2.1.6.1 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.3.4).

2.1.7 Lead (II) complexes with the following Compounds:

2.1.7 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo [8.5.2]heptadecane (1.3.3.4).

2.1.8 Mercury (II) complexes with the following Compounds:

2.1.8.1 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo [8.5.2]heptadecane (1.3.3.4).

2.1.9 Nickel (II) complexes with the following Compounds:

2.1.9.1 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).

2.1.10 Calcium (II) complexes with the following Compounds:

2.1.10.1. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).

2.1.10.2. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).

2.1.11 Magnesium (II) complexes with the following Compounds:

2.1.11.1. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).

**2.1.11.2. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).**

**2.2 Synthesis of Radioactive Complexes**

5 Water soluble salts of radioisotopes of iron(III) and gadolinium or manganese (II) (e.g., chloride salts of Fe-59, Gd-153) and chelators described in Examples 1.3 were heated in water, alcohol or DMSO solvents followed by base addition to achieve neutral or basic pH. Complex formation was verified by radiochromatography. Employing this method the following complexes were  
10 synthesized.

**2.2.1 Complexes of Fe-59**

- 15 **2.2.1.1. N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.1).**
- 2.2.1.2. (R, R, R) N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.2).**
- 2.2.1.3. (S, S, S) N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.3).**
- 20 **2.2.1.4. (R, R, R) N,N',N"-Tris(2-hydroxy-3-isobutoxypropyl)-1,4,7-triazacyclononane (1.3.1.5).**
- 2.2.1.5. N,N',N"-Tris(2-hydroxy-3-methoxypropyl)-1,4,7-triazacyclononane (1.3.1.6).**
- 25 **2.2.1.6. N,N',N"-Tris(2,3-dihydroxypropyl)-1,4,7-triazacyclononane (1.3.1.7).**
- 2.2.1.7. N,N',N"-Tris(2-hydroxy-2,2-diisopropoxyloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).**
- 2.2.1.8. N,N',N"-Tris(3-hydroxy-1,5-dioxacycloheptyl-3-methyl)-1,4,7-triazacyclononane (1.3.1.15).**
- 30 **2.2.1.9. N,N',N"-Tris[(3-hydroxy-7,7-dimethyl-1,5-dioxacyclooct-3-yl)-methyl]-1,4,7-triazacyclononane (1.3.1.16).**

- 2.2.1.10. N,N',N"-Tris[(3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.18).
- 2.2.1.11. N,N',N"-Tris[(3-hydroxy-1,5-dioxacyclooctane-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.20).
- 5 2.2.1.12. N,N',N"-Tris(2-hydroxy-2-methylpropyl)-1,4,7-triazacyclononane (1.3.1.21).
- 2.2.1.13. N,N',N"-Tris[(2,3-dihydroxy-2-ethylbutyl)]-1,4,7-triazacyclononane (1.3.1.26).
- 2.2.1.14. N,N',N"-Tris[2-hydroxy-2,2-bis(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.28).
- 10 2.2.1.15. N,N',N"-Tris(2-hydroxypropyl)-1,4,7-triazacyclononane (1.3.1.30).
- 2.2.1.16. N,N',N"-Tris(dihydroxyphosphorylmethyl monobutyl ester)-1,4,7-triazacyclononane (1.3.2.2).
- 2.2.1.17. N,N',N"-Tris(dihydroxyphosphorylmethyl monoethyl ester)-1,4,7-triazacyclononane (1.3.2.4).
- 15 2.2.1.18. 4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.3.3).
- 2.2.1.19. N,N',N"-Tris(dihydroxyphosphorylethyl)-1,4,7-triazacyclononane (1.3.3.5).
- 20 2.2.1.20. N,N',N",N'''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane (1.3.3.6).
- 2.2.1.21. 4,10-Bis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.3.7).
- 2.2.1.22. N,N',N"-Tris{[(diethylphosphoryl)- $\alpha$ -hydroxy]ethyl}-1,4,7-triazacyclononane (1.3.4.2).
- 25 2.2.1.23. N,N',N"-Tris[(N-methyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.2).
- 2.2.1.24. N,N',N"-Tris[(N-isopropyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.4).
- 30 2.2.1.25. N,N',N"-Tris[(N-t-butyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.6).

- 2.2.1.26. 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).
- 2.2.1.27. N,N',N"-Tris(carboxyethyl)-1,4,7-triazacyclononane (1.3.6.10).
- 2.2.1.28. N,N',N"-Tris[N-n-butyl(methylcarboxamide)]-1,4,7-  
5 triazacyclononane (1.3.10.2).
- 2.2.1.29. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.2.1.30. N,N'-Bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (1.3.12.3).
- 10 2.2.1.31. N-(carboxymethyl)-N',N"-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (1.3.12.4).
- 2.2.2 Complexes of Mn-54
- 15 2.2.2.1 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).

### EXAMPLE 3

20 This example illustrates the ability of the chelating agents described above to inhibit cell replication *in vitro*.

#### 3.1: INHIBITION OF BACTERIAL REPLICATION

25 This example demonstrates the ability of a representative example of the claimed ligands to inhibit replication of various bacteria *in vitro*.

N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695. Studies were performed to determine its ability to inhibit bacterial growth. For *Streptococcus hemolyticus*, *Listeria monocytogenes*, *Enterobacter cloacae* and  
30 *Klebsiella pneumoniae* the minimum inhibitory concentration was determined to be 0.15mM/L. For *Enterococcus faecalis*, *Pseudomonas aeruginosa* and

*Acinobacter anitratus* the minimum inhibitory concentration was determined to be 0.3mM/L.

### 3.2: INHIBITION OF MYCOTIC CELL REPLICATION IN VITRO

5 This example demonstrates the ability of a representative example of the claimed ligands to inhibit mycotic (fungal) cell replication *in vitro*.

N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695. Studies were performed to determine its ability to inhibit growth of mycotic (fungal) organisms.

10 For *Microsporum canis* the minimum inhibitory concentration was 0.233 mM/L or less. For *Candida albicans* and *Trichophyton rubrum* the minimal inhibitory concentration was 2.33 mM/L. For *Trichophyton mentagrophytes*, *Trichophyton tonsuras* and *Trichophyton violaceum* the 15 minimal inhibitory concentration was 23.3 mM/L.

### 3.3: INHIBITION OF MAMMALIAN CELL REPLICATION IN VITRO

This example demonstrates the ability of representative examples of the claimed ligands to inhibit mammalian cell replication *in vitro*.

20 N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695.

Concentrations of this ligand of 0.009 mM/L inhibited the growth of both BGM cells (a continuous cell line of monkey origin) and HFF cells (human foreskin fibroblasts).

25 N,N',N"-Tris(carboxymethyl)-1,4,7-Triazacyclononane (Example 1.3.6.1) at a concentration of 0.009 mM/L inhibited BGM cell growth and a concentration of 0.019 mM/L inhibited HFF cell growth.

30 N,N',N"-Tris(ethoxycarbonylmethyl)-1,4,7-Triazacyclononane (Example 1.3.6.13) at a concentration of 0.04 mM/L inhibited BGM cell growth and at a concentration of 0.16 mM/L inhibited HFF cell growth. Diethylene triamine penta acetic acid at a concentration of 0.075 mM/L inhibited BGM cell growth and at 0.3 mM/L inhibited HFF cell growth.

**EXAMPLE 4**

This example demonstrates the relative lack of toxicity of a representative example of the claimed ligands toward nonproliferating mammalian cells *in vitro*.

N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695.

A concentration of 0.3mM of this agent was added to mature, nonreplicating cultures of HFF (human foreskin fibroblasts) kept in maintenance media and no effect on the resting cells was observed over a five-day period of observation.

**EXAMPLE 5**

This example illustrates the low *in vivo* toxicity of a representative ligand administer intravenously to mice.

Over 50% of mice receiving 4.0mM/kg intravenously of the sodium salt of N,N',N"-tris-(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (Example 1C in U.S. Patent No. 5,236,695) as a single intravenous dose survived for over 14 days following such administration demonstrating that the acute LD50 of this agent is in excess of 4mM/kg. This *in vivo* LD50 toxicity dose results in an instantaneous *in vivo* concentration which is orders of magnitude greater than the dose of this agent which inhibits mammalian cell replication *in vitro* (0.009mM/L).

**EXAMPLE 6**

This example demonstrates the relatively low subacute toxicity of a representative ligand administered intravenously in repeated doses to rats.

Ten male Sprague Dawley rats 29 days old and weighing between 73.4 and 87.8 grams at the beginning of the experiment were randomized, employing the block stratification method, into two groups consisting of five

rats each. On each of days 1, 2, 3, 6, 7, 8, 9, 10, 13 and 14 of the experiment one set of rats received an intravenous dose of N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7- triazacyclononane (Example 1C in U.S. Patent No. 5,236,695) equal to 0.05 millimoles per kg of initial body weight  
5 (experimental group) while the other group received an equivalent volume of normal saline solution. The weights of the animals were recorded three times per week and the animals were sacrificed on the 28th day, major organs removed and weighed and tissues removed for microscopic examination. There was no statistically significant difference in weight or rate of weight gain  
10 between the experimental and control group of rats, either during the period of injections or in the two-week post-injection period. There were no differences observed between the weights of major organs of the experimental vs. the control group. There were no differences between the tissues of the experimental vs. the control group upon microscopic examination of the tissues  
15 obtained at the time of necropsy.

#### EXAMPLE 7

This example illustrates the *in vivo* distribution of radioisotopic  
20 complexes

Examples of the *in vivo* distribution of radioisotopic complexes of representative ligands are herein disclosed which demonstrate the ability of these agents to be predominantly excreted by the kidneys, or the liver, or to pass across cell membranes and accumulate in the intracellular fluid space (e.g.  
25 in heart muscle). Those skilled in the art will recognize that a similar *in vivo* distribution can be anticipated from non-radioisotopic paramagnetic complex species.

In the following examples certain radioisotopic complexes of the subject ligands were administered intravenously to mice and the tissue  
30 distribution of the radioisotopic complexes was measured by detection of radioisotopic content of tissues removed at necropsy.

**6.1: EXAMPLE OF A COMPLEX WHICH IS PREDOMINANTLY EXCRETED BY THE KIDNEYS IN THE URINE**

The iron-59 labeled complex of N,N',N'-tris(2,3-dihydroxy propyl)-1,4,7-triazacyclononane (Example 2.2.1.6) was administered intravenously to mice and at necropsy the tissue distribution of radioactivity showed predominant concentration of the agent in the kidneys and urine.

**6.2: EXAMPLE OF A COMPLEX WHICH IS PREDOMINANTLY EXCRETED BY THE LIVER IN THE BILE.**

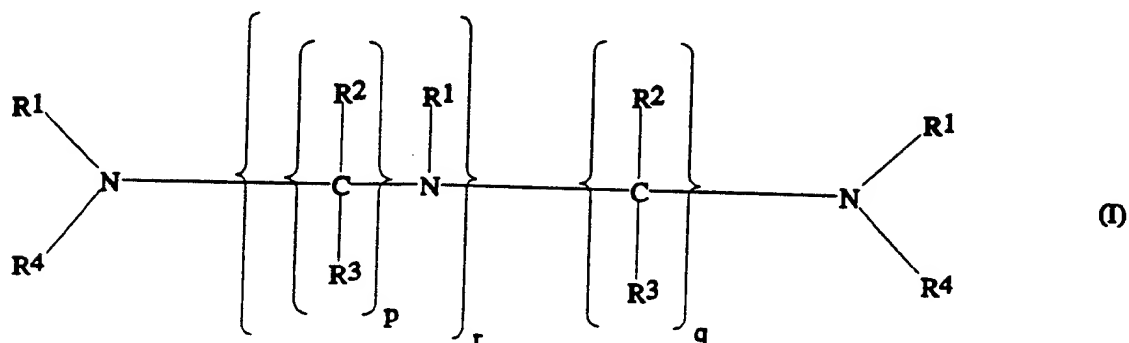
The iron-59 complex of N,N',N"- tris(2'-hydroxy-3-iso-propoxypropyl)-1,4,7-triazacyclononane (Example 2.2.1.1) was administered intravenously to mice and at necropsy the tissue distribution of radioactivity showed predominant concentration of the agent in the liver, bile and intestinal contents.

**6.3: EXAMPLE OF A COMPLEX WHICH RAPIDLY PASSES ACCROSS CELL MEMBRANES AND ENTERS THE INTRACELLULAR FLUID SPACE**

The iron-59 complex of N,N',N"-tris[2-hydroxy-(2,2-diisopropoxyloxymethyl)ethyl]-1,4,7-triazacyclononane (Example 2.2.1.7) was administered intravenously to mice and at necropsy the tissue distribution of activity was consistent with an intracellular as well as extracellular fluid distribution. Within the first five minutes following agent administration the concentration of activity in the heart was greater than that of mixed venous blood indicating rapid equilibration of the agent across myocardial cell membranes. The liver concentrated the agent and excreted it into the bile.

**WHAT IS CLAIMED IS:**

1. A method for inhibiting bacterial or fungal growth on a surface or in a solution comprising administering to said surface or solution a complexing agent having the formula:



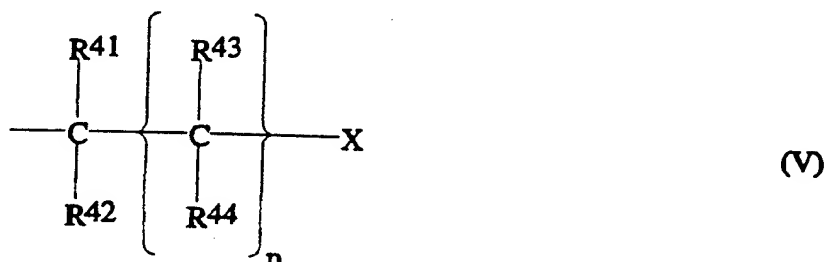
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



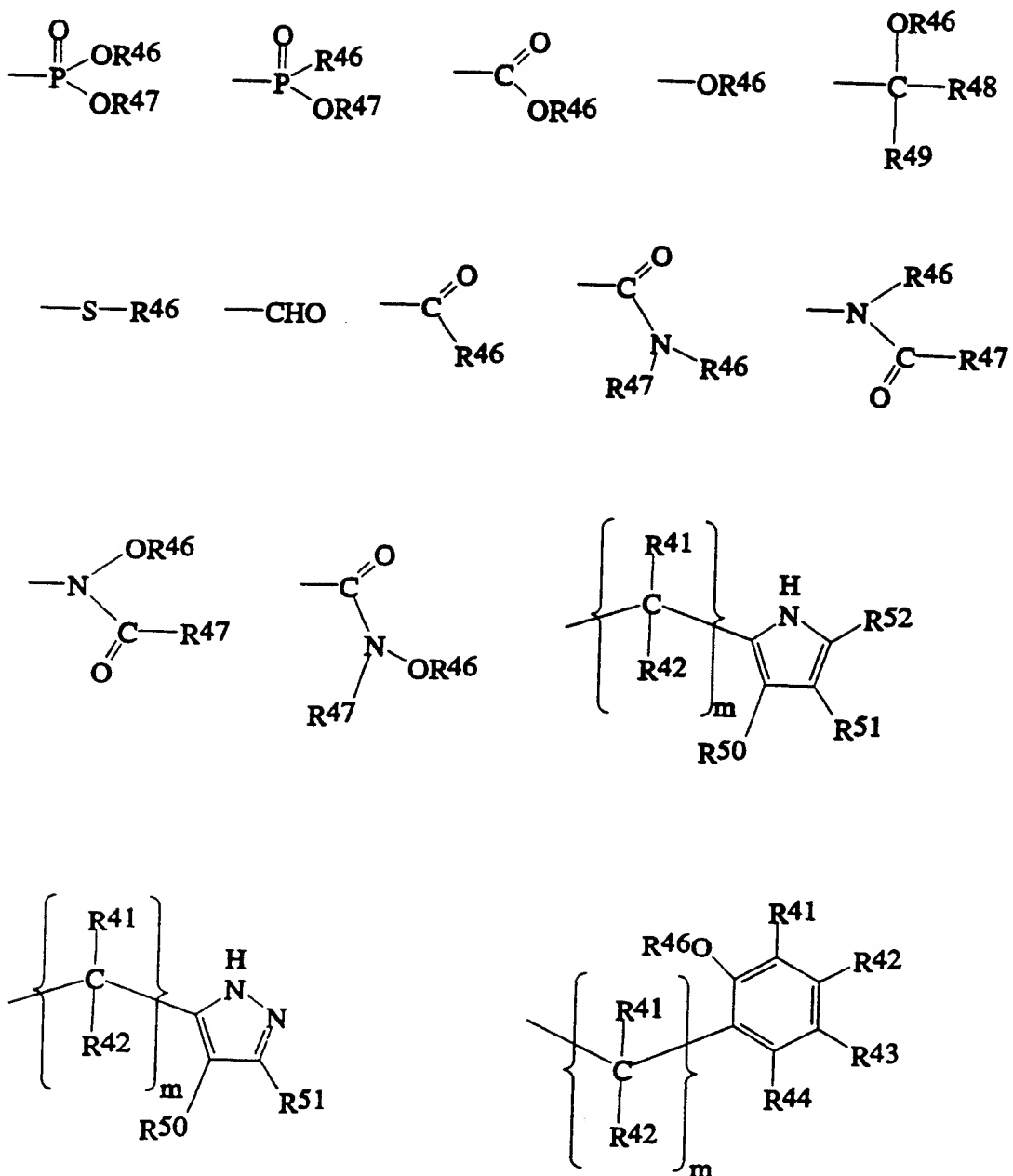
wherein,

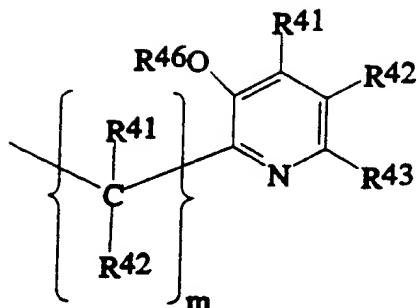
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy,

alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;  $R^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

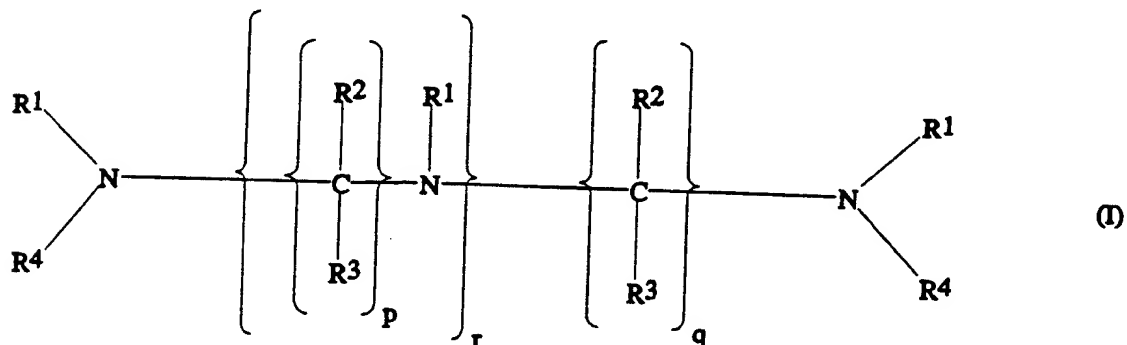
*m* is an integer of from 1 to 3,

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms; and physiological salts thereof with the proviso that the molecular weight of said complexing agent does not exceed 2000.

2. A method in accordance with claim 1, wherein said surface is a human body surface.

3. A method in accordance with claim 1, wherein said complexing agent is added to a solution.

4. A method for treating conditions dependent on the bioavailability of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:



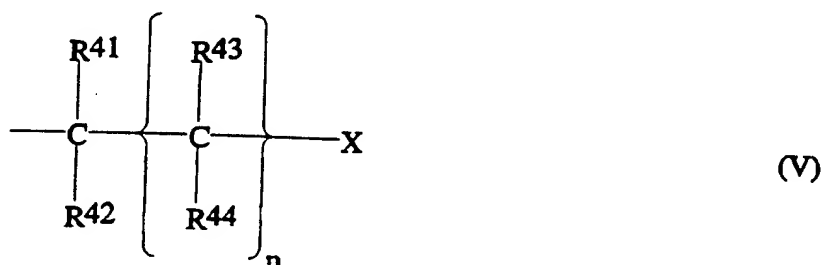
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



wherein,

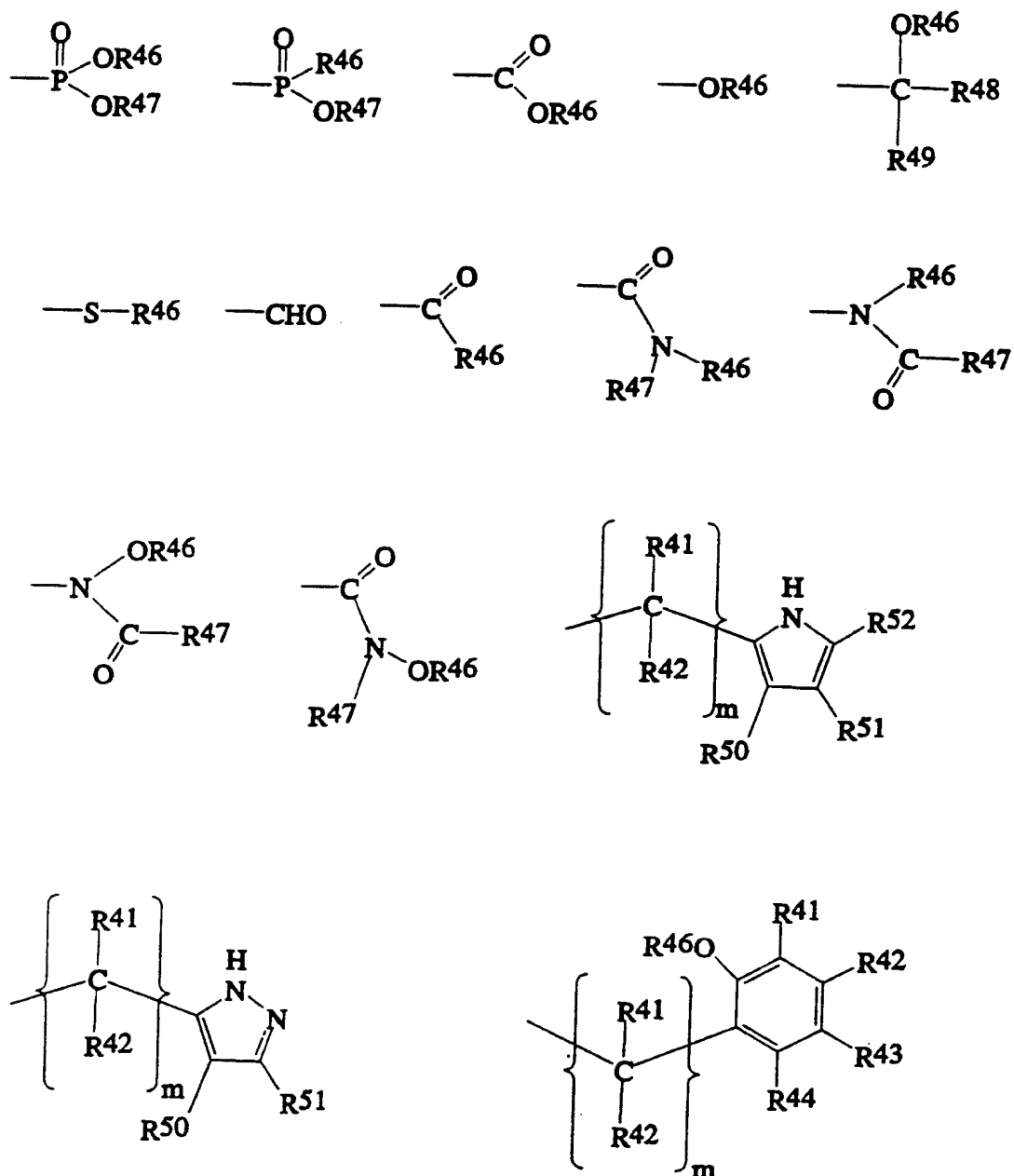
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group

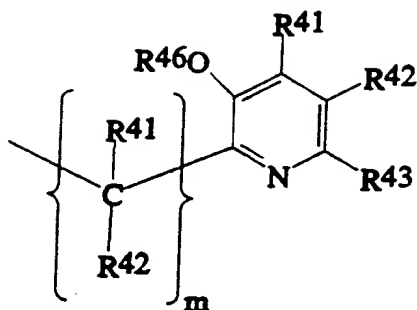
consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

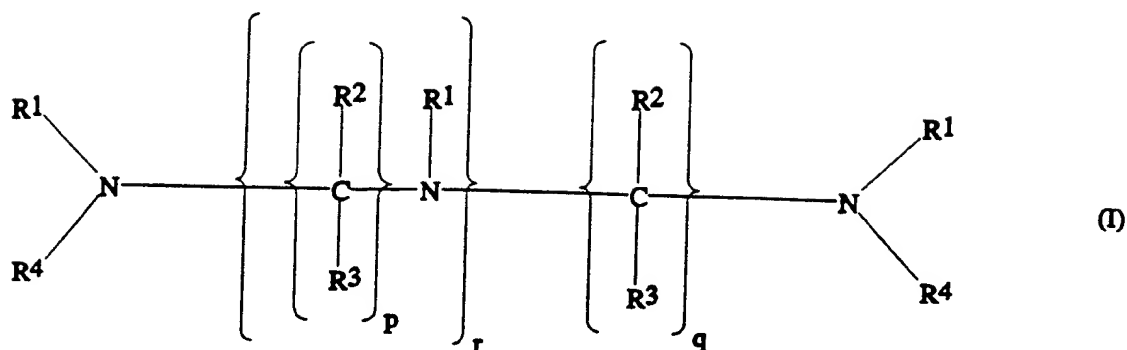
R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said complexing agent does not exceed 2000; and said complexing agent is present in a pharmaceutically acceptable carrier.

5. A method for treating conditions associated with elevated levels of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:



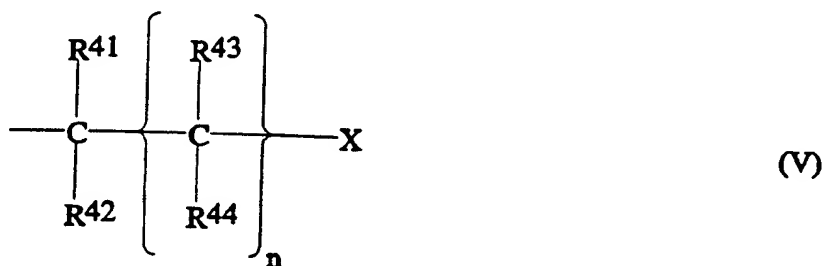
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



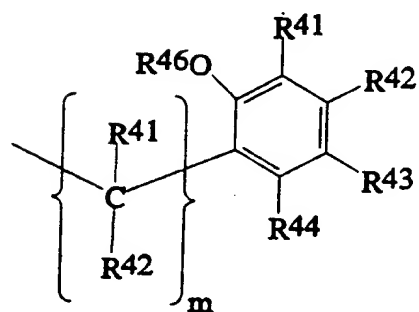
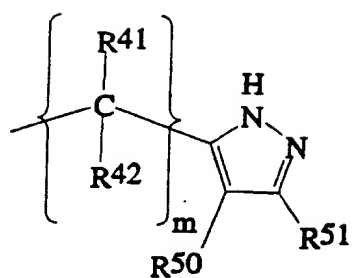
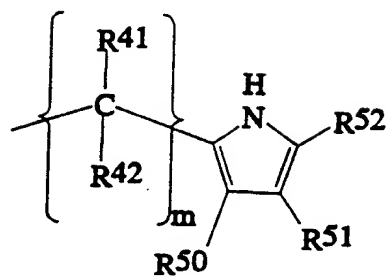
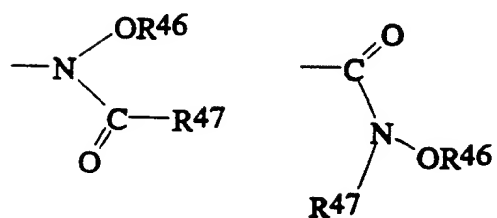
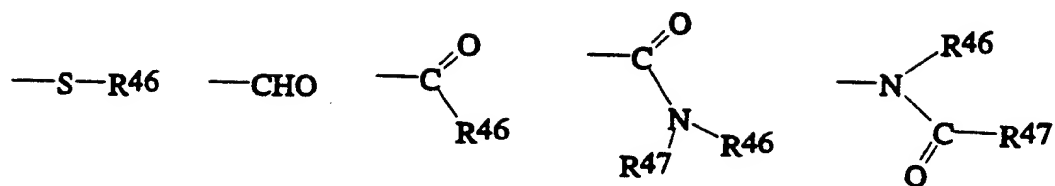
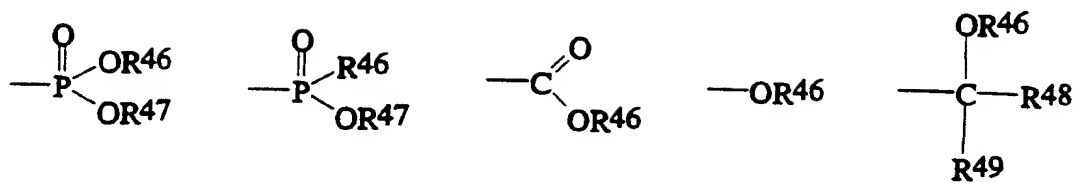
wherein,

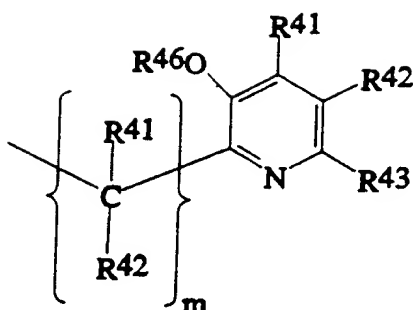
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl

interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;  
 $R^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and *m* is an integer of from 1 to 3;

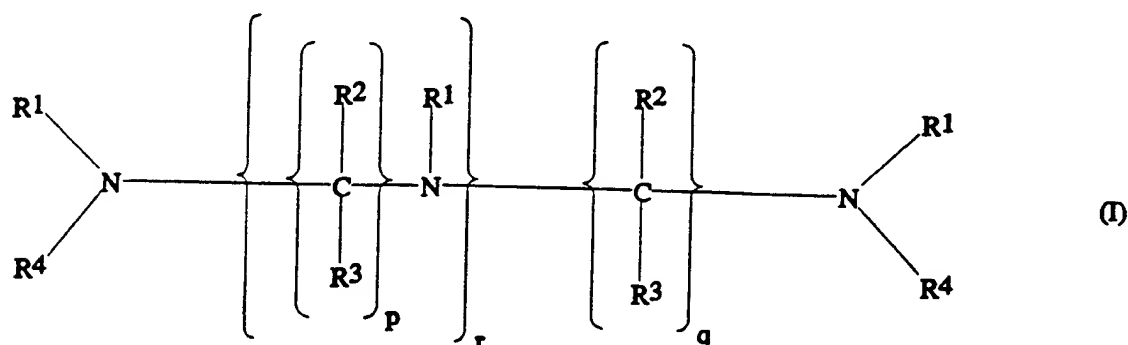
and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms; and physiological salts thereof, with the proviso that at least one R<sup>1</sup> group is other than a radical of formula (V) in which X is carboxylic acid and with the further proviso that the molecular weight of said complexing agent does not exceed 2000; and said complexing agent is present in a pharmaceutically acceptable carrier.

6. A method in accordance with claim 4 wherein said conditions are mediated by proliferation of DNA or RNA viruses.

7. A method in accordance with claim 4 wherein said conditions are mediated by cell proliferation.
8. A method in accordance with claim 7 wherein said condition is neoplasia.
9. A method in accordance with claim 7 wherein said condition is a bacterial infection.
10. A method in accordance with claim 7 wherein said condition is a fungal infection.
11. A method in accordance with claim 7 wherein said condition is a protozoal infection.
12. A method in accordance with claim 7 wherein said condition is an inflammatory condition.
13. A method in accordance with claim 7 wherein said condition is an immune disorder.
14. A method in accordance with claim 7 wherein said condition is a pregnancy termination.
15. A method in accordance with claim 7 wherein said condition is a condition further mediated by osteoclast proliferation.
16. A method in accordance with claim 4 wherein said conditions are mediated by free radical or oxidation related tissue destruction.
17. A method in accordance with claim 16 wherein said conditions are selected from the group consisting of rheumatoid arthritis and related disorders.
18. A method in accordance with claim 5, wherein said conditions are selected from the group consisting of hemochromatosis, hemosiderosis and Wilson's disease.

19. A method in accordance with claims 1, 4 or 5, wherein at least two of said  $R^1$  are selected from the group consisting of phosphonic acid-containing radicals, phosphonic acid mono ester-containing radicals, carboxylic acid-containing radicals and combinations thereof.

20. A method for nuclear medical imaging or enhancing contrast in magnetic resonance imaging in a patient, said method comprising;  
administering to said patient a pharmaceutical composition comprising a radioisotopic or paramagnetic first transition series element which is in chelated form with a compound of formula:



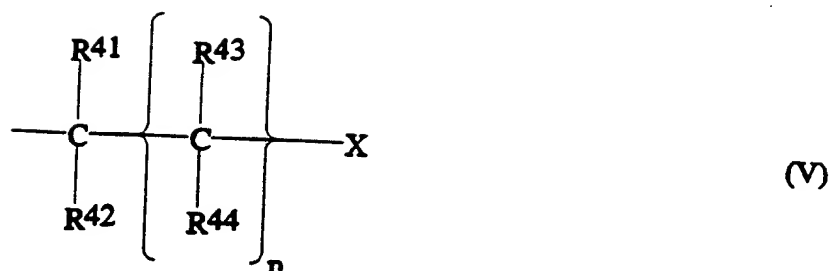
wherein,

$p$  and  $q$  are each independently integers of from 2 to 3;

$r$  is an integer of from 0 to 4;

$R^2$ ,  $R^3$  and  $R^4$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^1$  is a member selected from the group consisting of  $R^2$ ,  $R^3$ ,  $R^4$ , and radicals of formula:

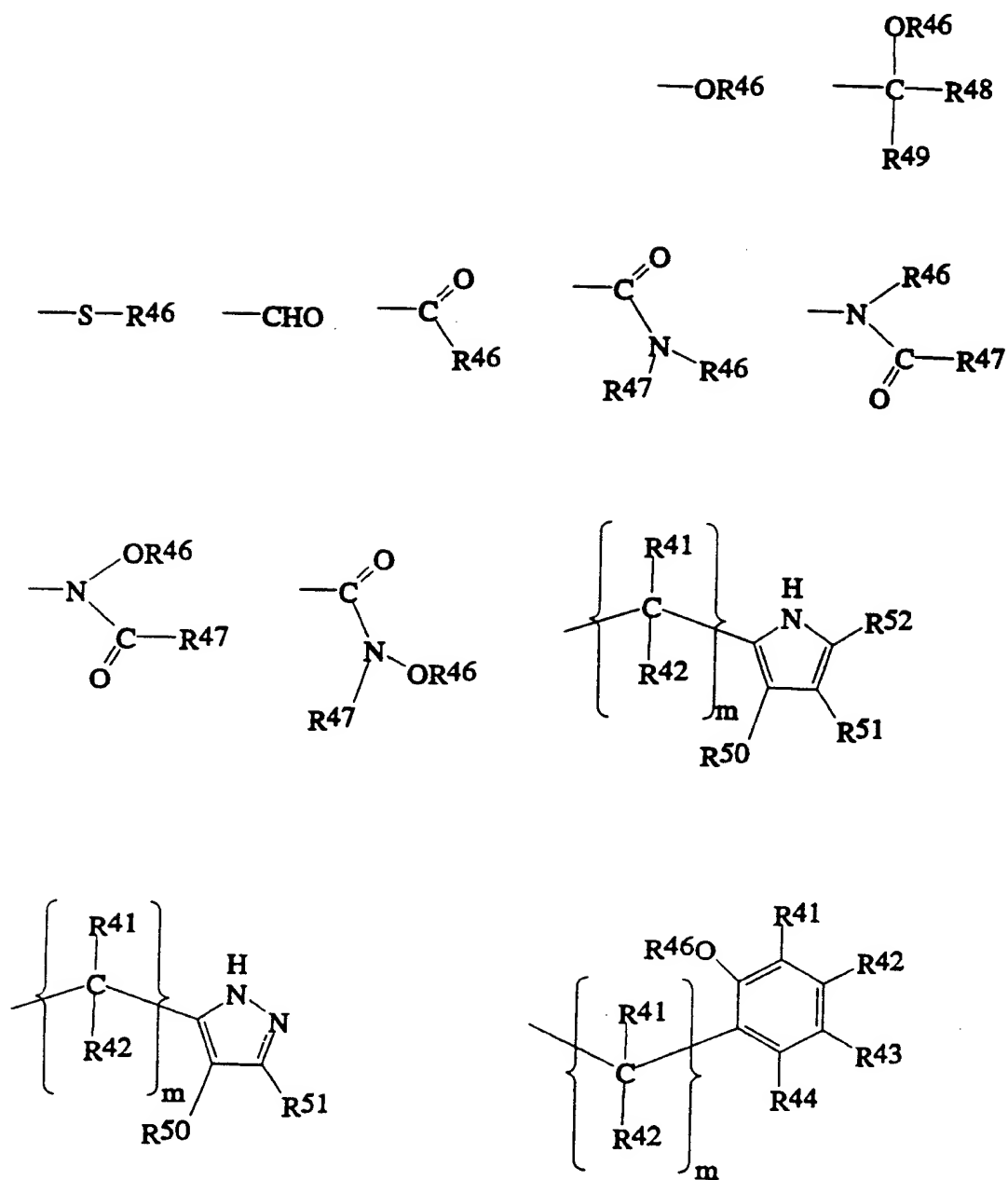


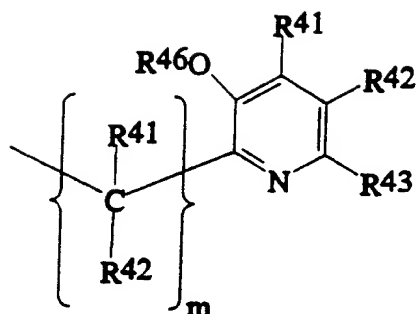
wherein,

$\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;  
 $\text{R}^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$n$  is zero or 1; and

$X$  is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

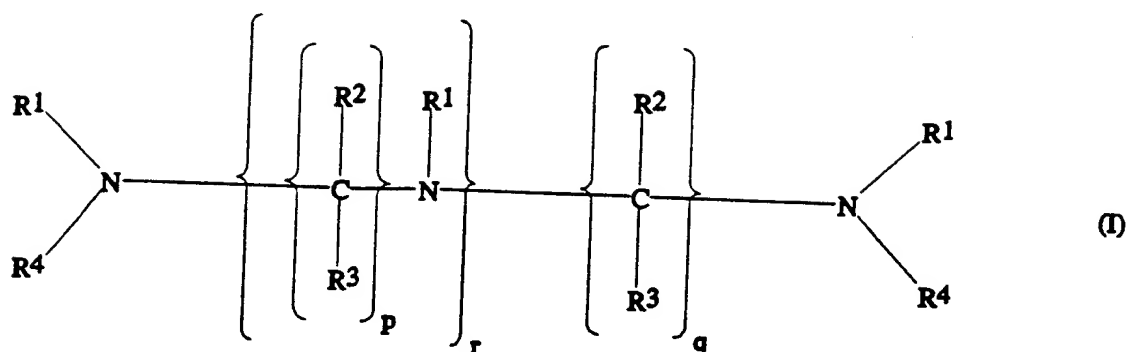
R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms, with the proviso that the molecular weight of said compound does not exceed 2000; and detecting said radioisotopic or paramagnetic first transition series element.

21. A pharmaceutical composition comprising a compound of the formula:



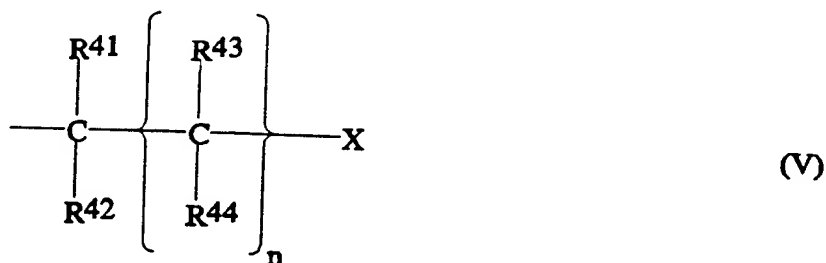
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



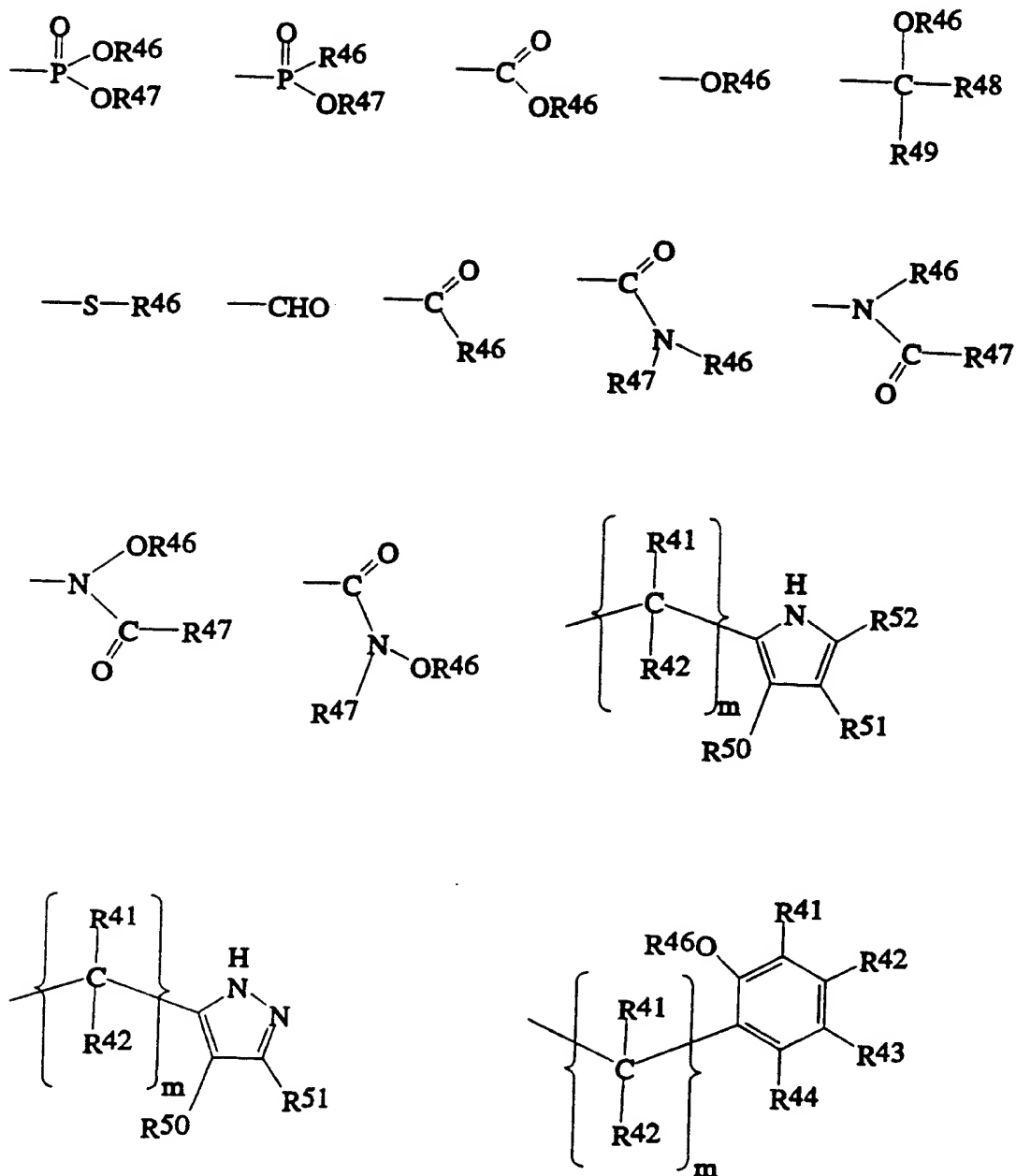
wherein,

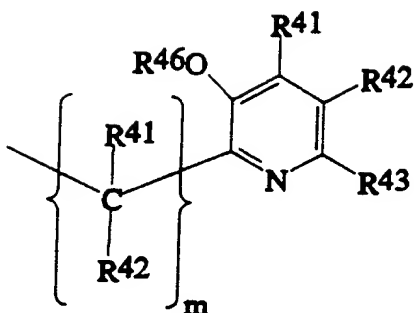
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl,

hydroxyarylalkyl, and halogen substituted versions thereof;  
 $R^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

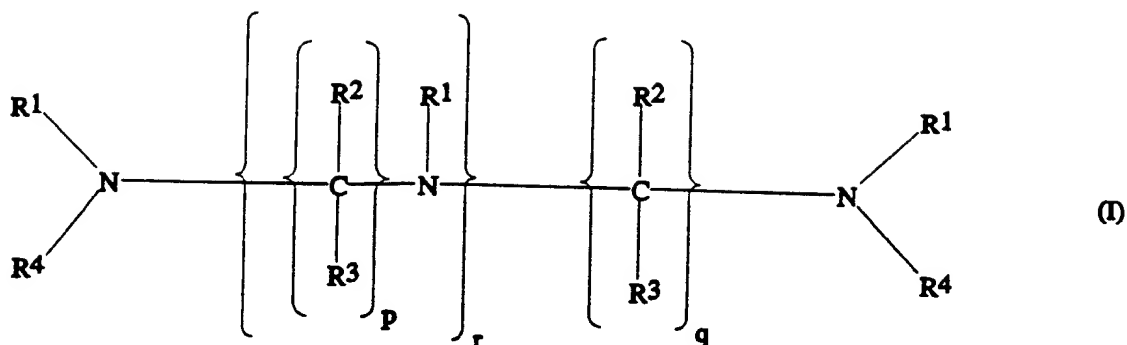
R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and  
m is an integer of from 1 to 3,

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms; and  
physiological salts thereof with the proviso that at least one R<sup>1</sup> group is other than a radical of formula (V) in which X is carboxylic acid and with the further proviso that the molecular weight of said compound does not exceed 2000; in a pharmaceutically acceptable carrier.

22. Compounds having the formula:

149



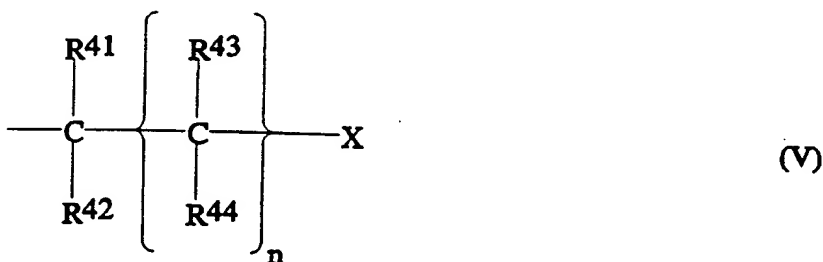
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



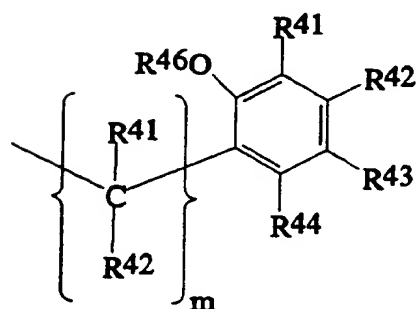
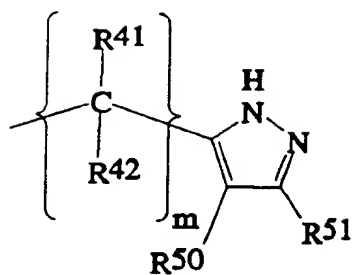
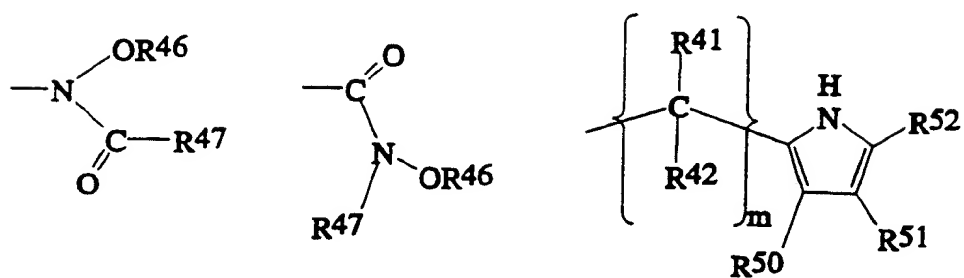
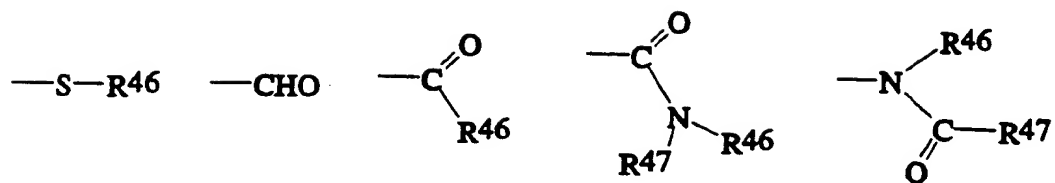
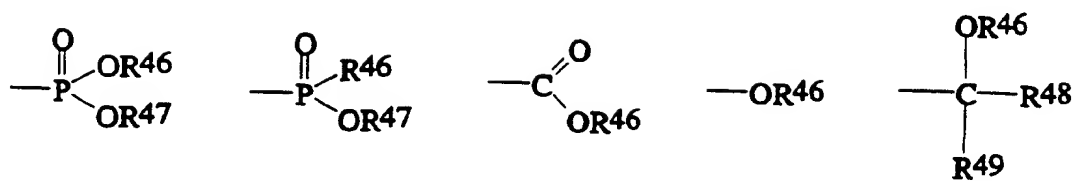
wherein,

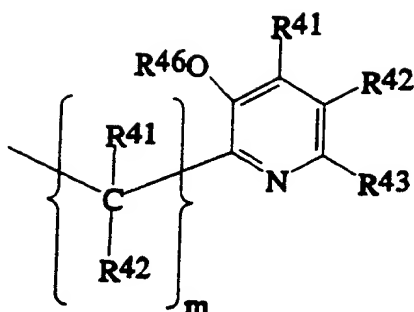
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl,

hydroxyarylalkyl, and halogen substituted versions thereof;  
R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and m is an integer of from 1 to 3,

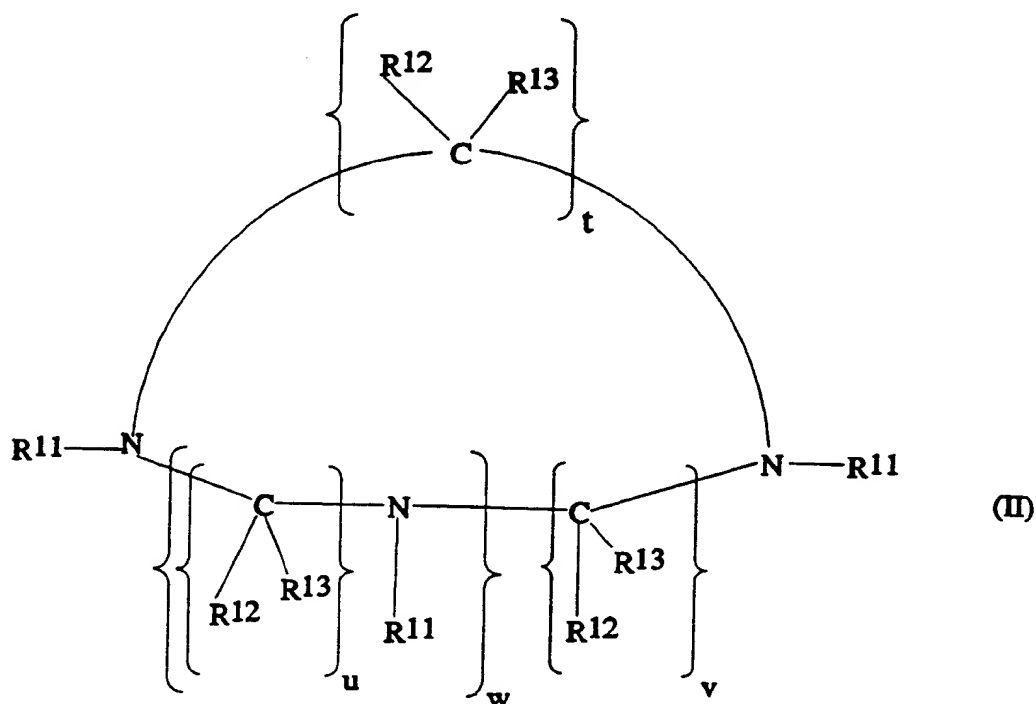
and wherein at least two of said R<sup>1</sup> and R<sup>4</sup> groups comprise at least two contiguous carbon atoms directly attached to nitrogen atoms and the carbon atom in a position  $\beta$  to the nitrogen atom is substituted with a hydroxy and at least one member selected from the group consisting of hydroxymethyl, alkoxymethyl, alkenoxymethyl, aryloxymethyl and combinations thereof;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said compound does not exceed 2000.

23. A compound in accordance with claim 22, wherein the cations of said physiological salts are sodium or N-methyl glucamine.

24. A method for inhibiting bacterial or fungal growth on a surface or in a solution comprising administering to said surface or solution a complexing agent having the formula:



wherein,

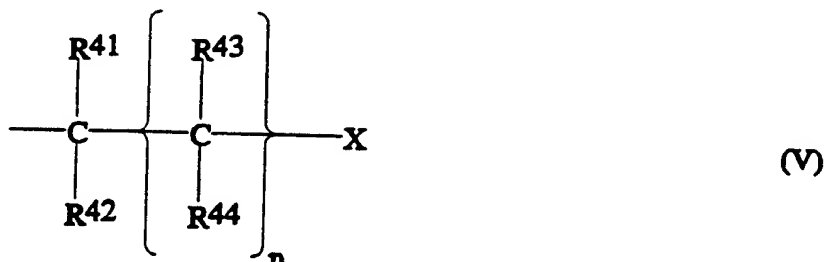
t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted

**versions thereof;**

**R<sup>11</sup> is a member selected from the group consisting of R<sup>12</sup>, R<sup>13</sup> and radicals of formula:**



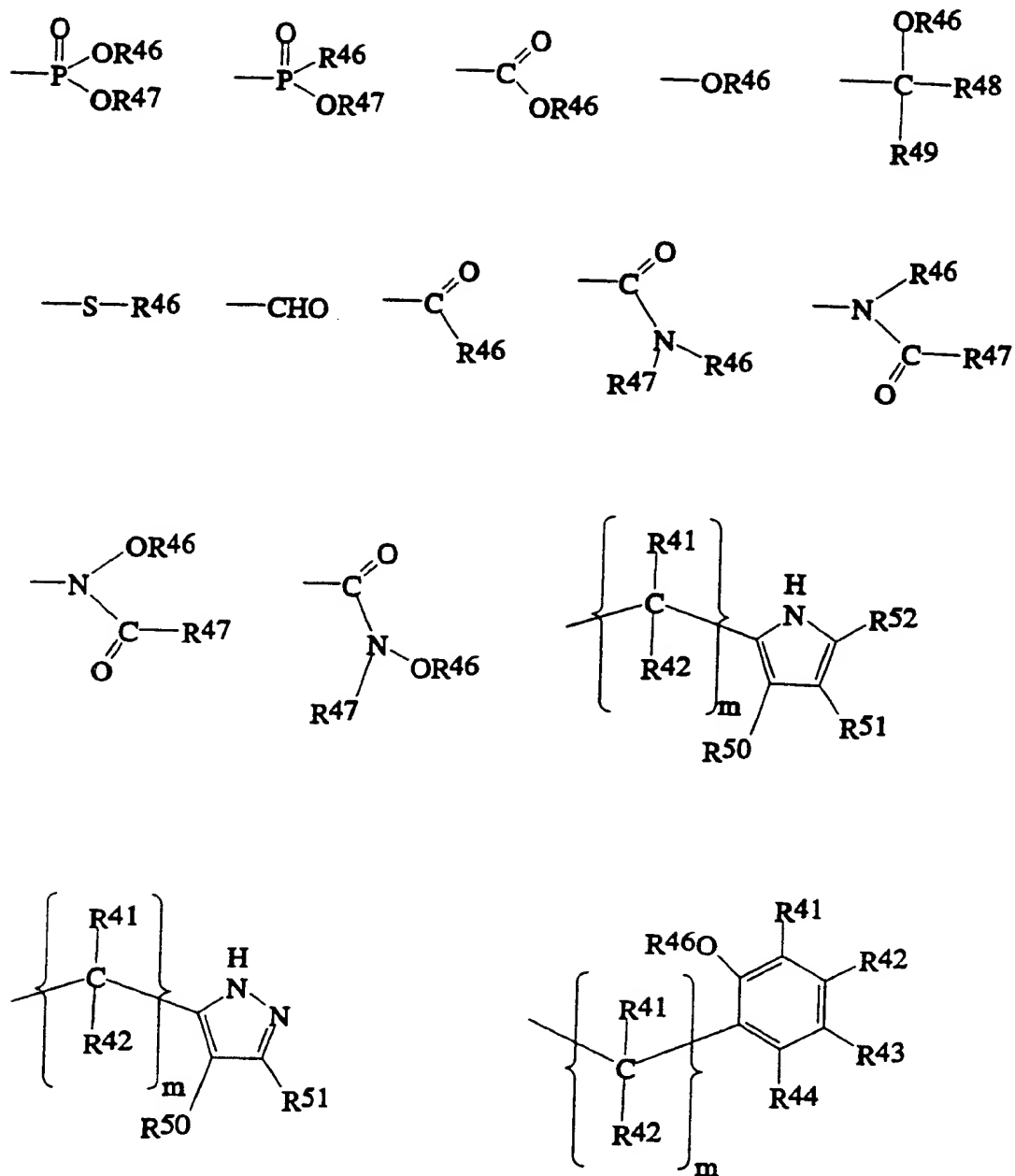
wherein,

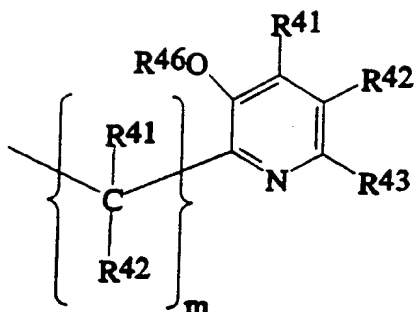
**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3,

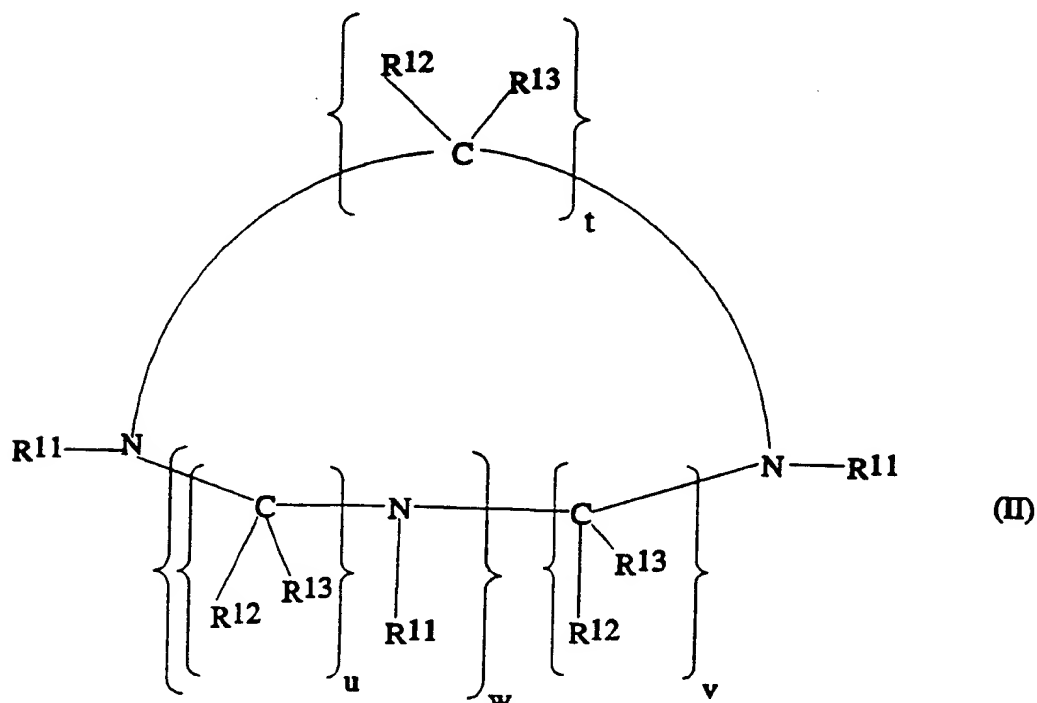
and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said complexing agent does not exceed 2000.

25. A method in accordance with claim 24, wherein said surface is a human body surface.

26. A method in accordance with claim 24, wherein said complexing agent is added to a solution.

27. A method for treating conditions dependent on the bioavailability of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:



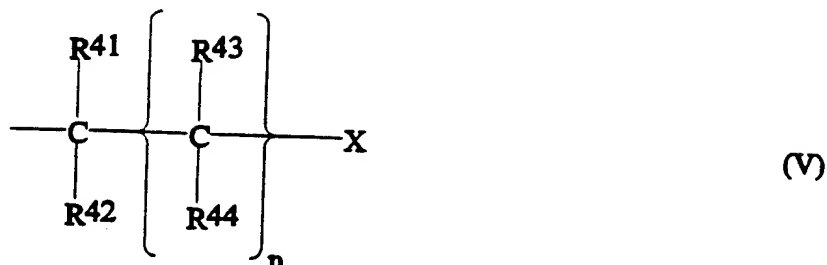
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^{11}$  is a member selected from the group consisting of  $R^{12}$ ,  $R^{13}$  and radicals of formula:

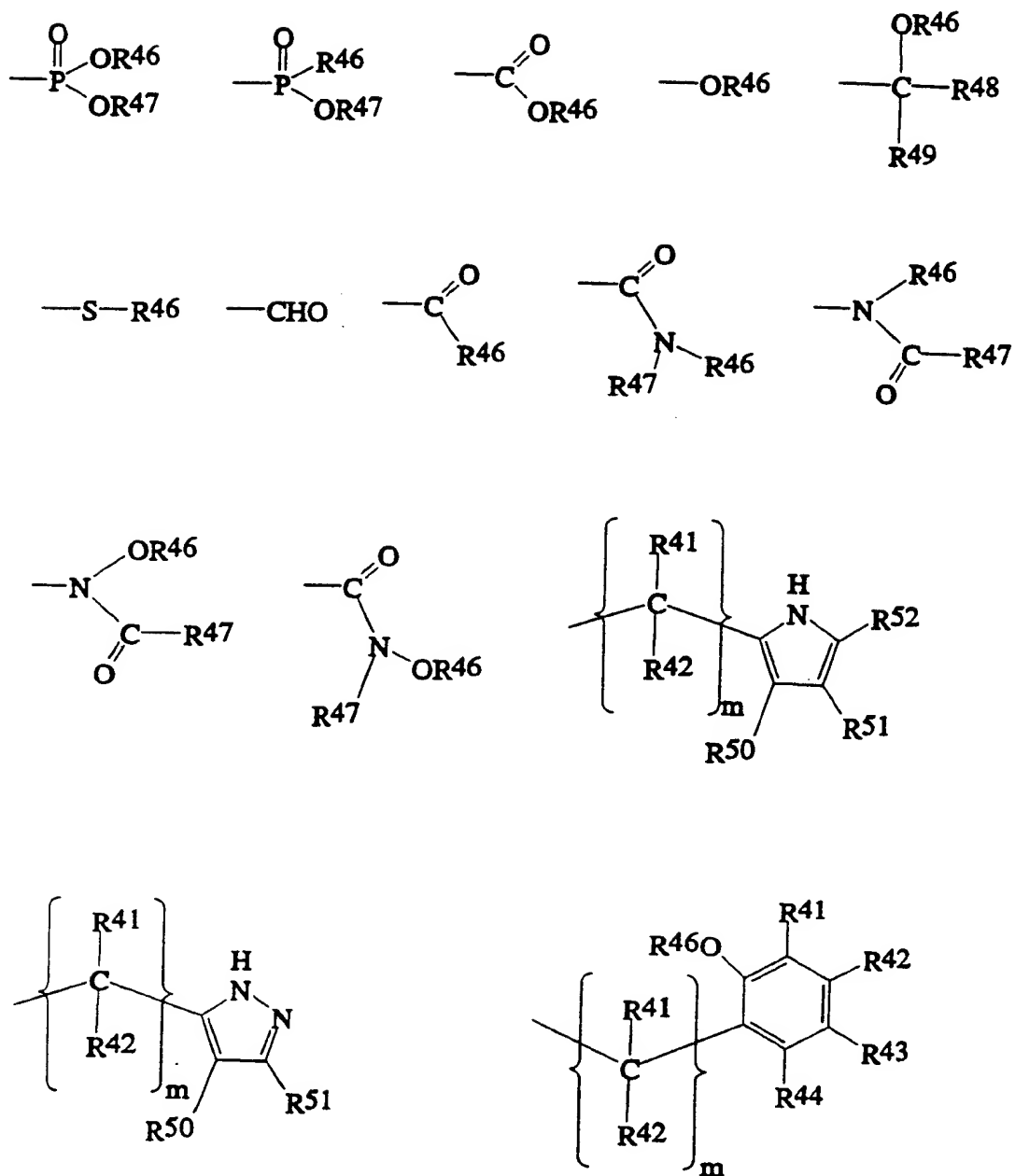


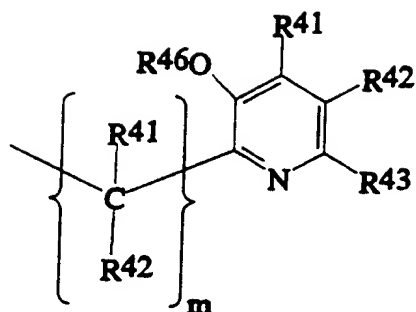
wherein,

$R^{41}$ ,  $R^{42}$  and  $R^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;  
 $R^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$n$  is zero or 1; and

$X$  is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

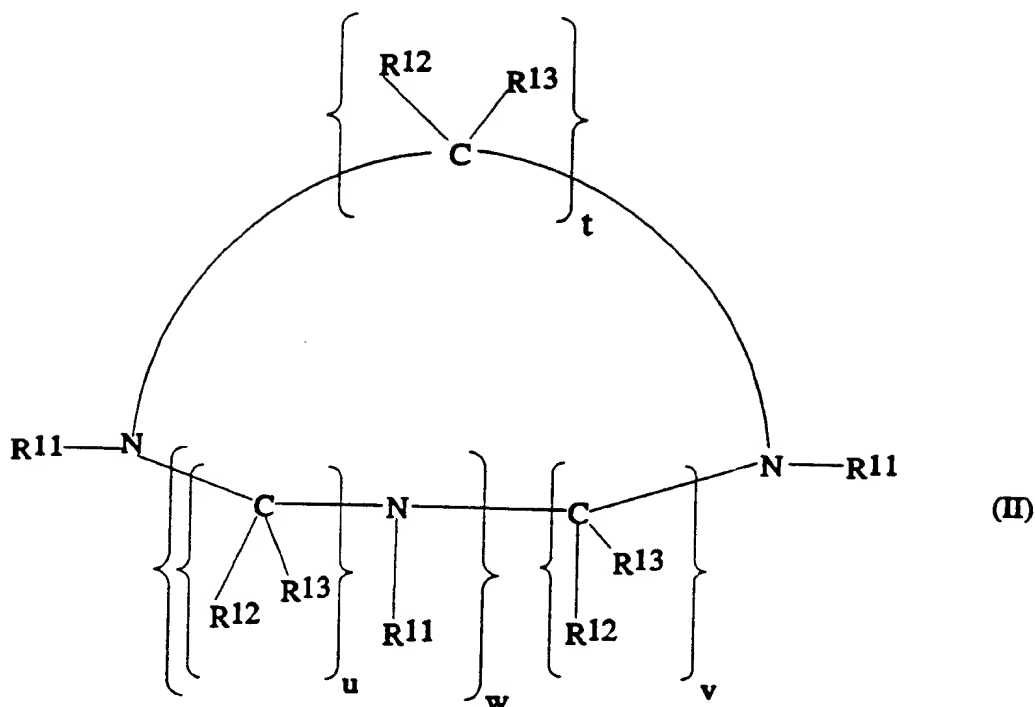
m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

with the proviso that the molecular weight of said complexing agent does not exceed 2000.

28. A method for treating conditions dependent on elevated levels of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:

161



wherein,

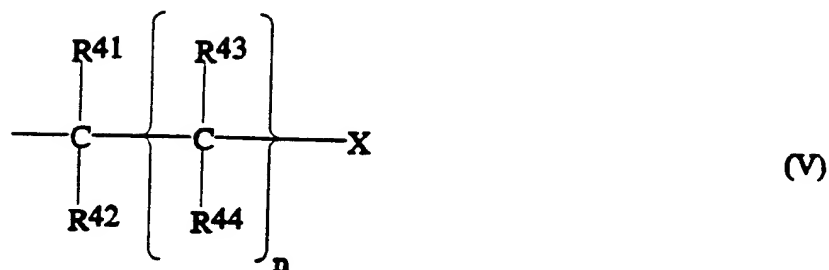
t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>11</sup> is a member selected from the group consisting of R<sup>12</sup>, R<sup>13</sup> and radicals of formula:

162



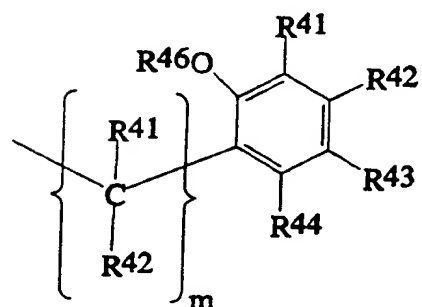
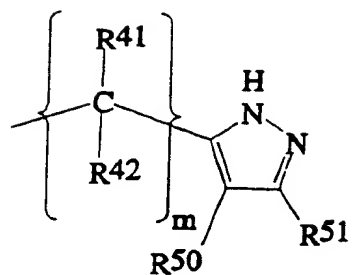
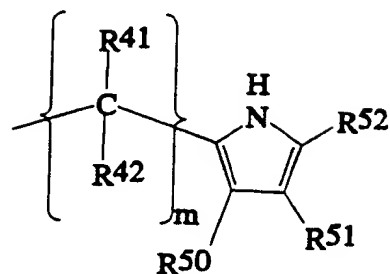
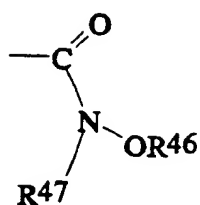
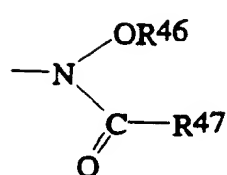
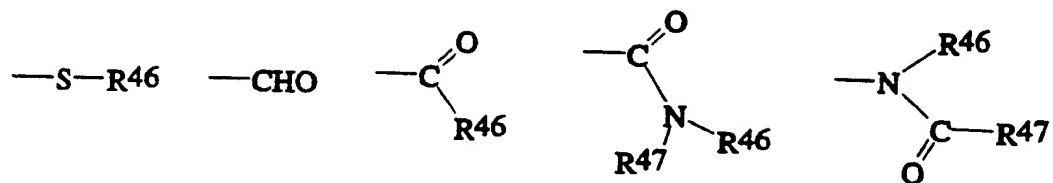
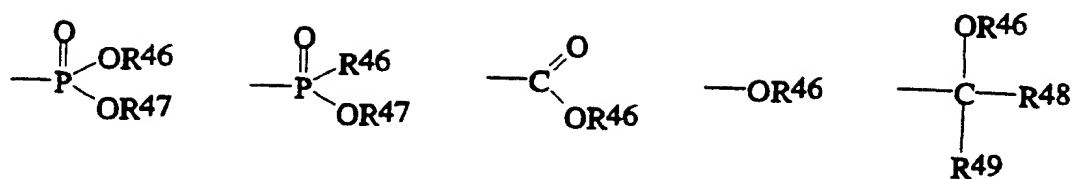
wherein,

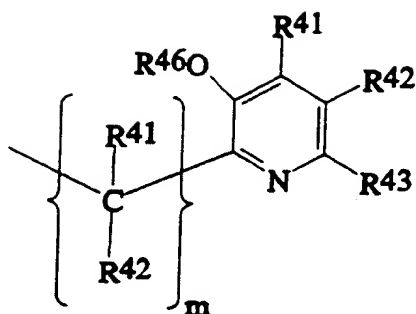
$\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

$\text{R}^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

*m* is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

with the proviso that the molecular weight of said complexing agent does not exceed 2000.

29. A method in accordance with claim 27 wherein said conditions are mediated by proliferation of DNA or RNA viruses.

**30.** A method in accordance with claim 27 wherein said conditions are mediated by cell proliferation.

**31.** A method in accordance with claim 30, wherein said condition is neoplasia.

**32.** A method in accordance with claim 30, wherein said condition is a bacterial infection.

**33.** A method in accordance with claim 30, wherein said condition is a fungal infection.

**34.** A method in accordance with claim 30, wherein said condition is a protozoal infection.

**35.** A method in accordance with claim 30, wherein said condition is an inflammatory condition.

**36.** A method in accordance with claim 30, wherein said condition is an immune disorder.

**37.** A method in accordance with claim 30, wherein said condition is a pregnancy termination.

**38.** A method in accordance with claim 30, wherein said condition is a condition mediated by osteoclast proliferation.

**39.** A method in accordance with claim 27, wherein said conditions are mediated by free radical or oxidation related tissue destruction.

**40.** A method in accordance with claim 39, wherein said conditions are selected from the group consisting of rheumatoid arthritis and related disorders.

**41.** A method in accordance with claim 28, wherein said conditions are selected from the group consisting of hemachromatosis, hemosiderosis and Wilson's disease.

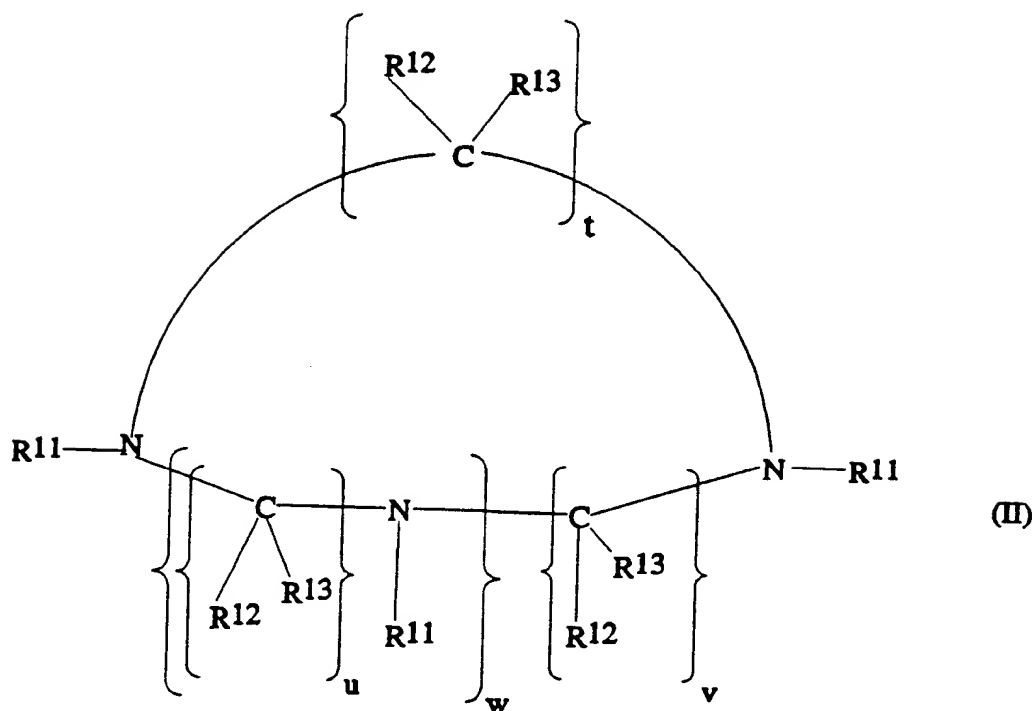
42. A method in accordance with claims 24, 27 or 28, wherein t, u and v are each 2, and w is 1.

43. A method in accordance with claim 42 wherein at least two of said R<sup>1</sup> are selected from the group consisting of phosphonic acid-containing radicals, phosphonic acid mono ester-containing radicals, carboxylic acid-containing radicals and combinations thereof.

44. A method in accordance with claims 24, 27 or 28 wherein t, u and v are each 2, and w is 2.

45. A method in accordance with claim 44 wherein at least two of said R<sup>1</sup> are selected from the group consisting of phosphonic acid-containing radicals, phosphonic acid mono ester-containing radicals, carboxylic acid-containing radicals and combinations thereof.

46. A method for nuclear medical imaging or enhancing contrast in magnetic resonance imaging in a patient, said method comprising;  
administering to said patient a pharmaceutical composition comprising a radioisotopic or paramagnetic first transition series element which is in chelated form with a compound of formula:



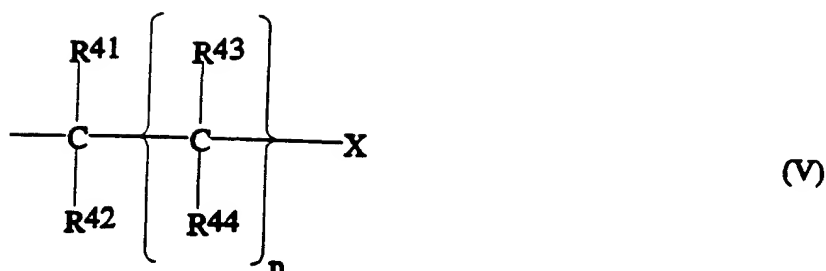
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

$R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^{11}$  is a member selected from the group consisting of  $R^{12}$ ,  $R^{13}$  and radicals of formula:



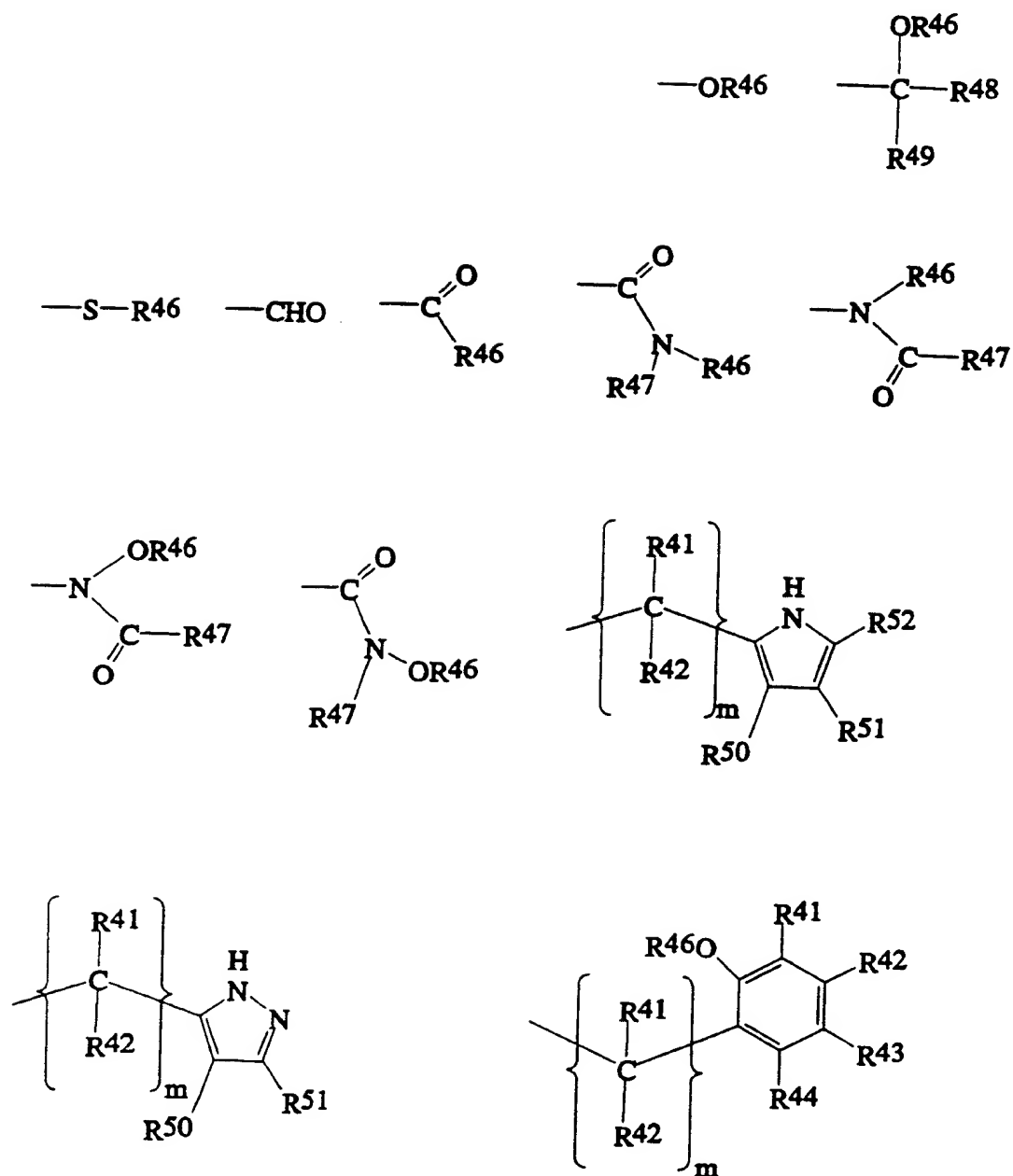
wherein,

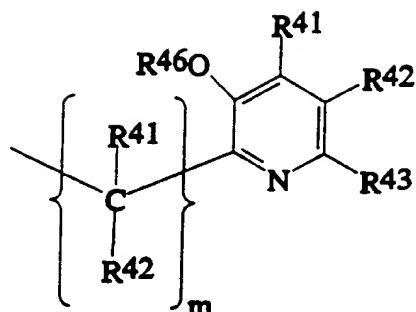
**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

**R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;**

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

*m* is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

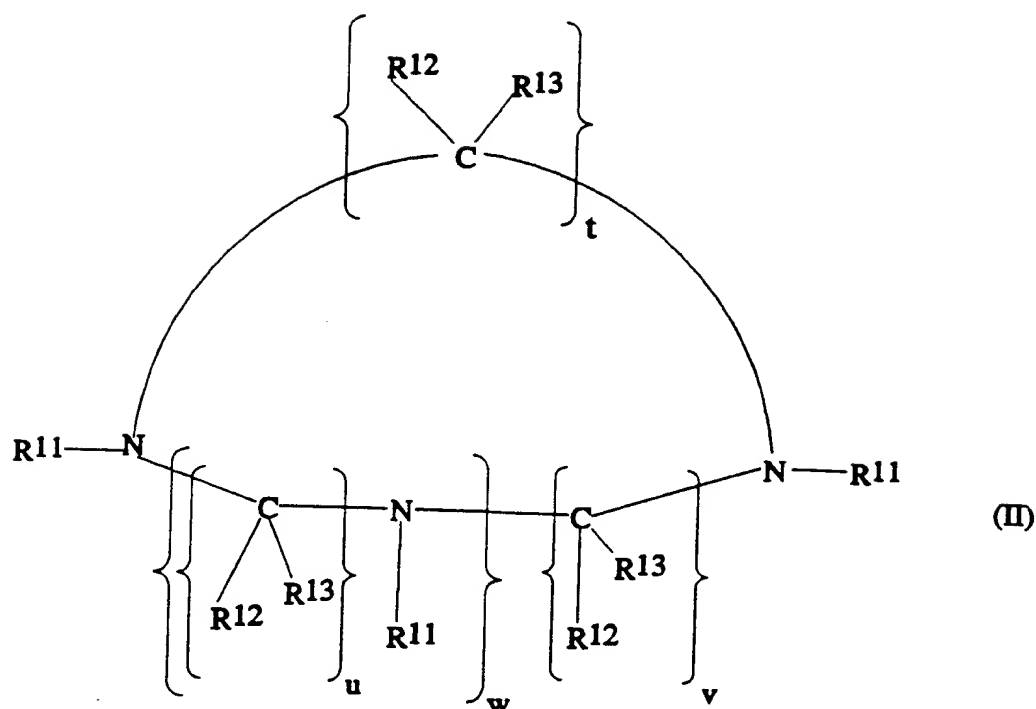
with the proviso that the molecular weight of said compound does not exceed 2000; and

detecting said radioisotopic or paramagnetic first transition series element.

47. A pharmaceutical composition comprising a compound having the

171

formula:



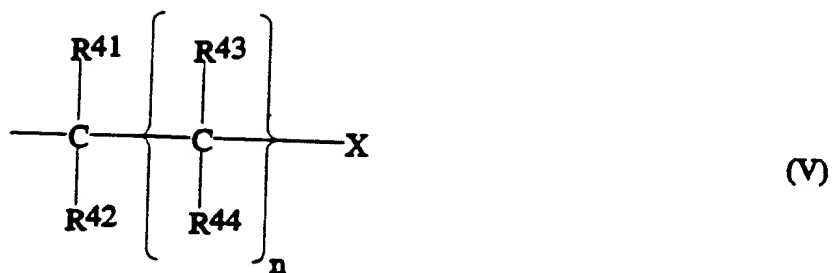
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

$R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^{11}$  is a member selected from the group consisting of  $R^{12}$ ,  $R^{13}$  and radicals of formula:



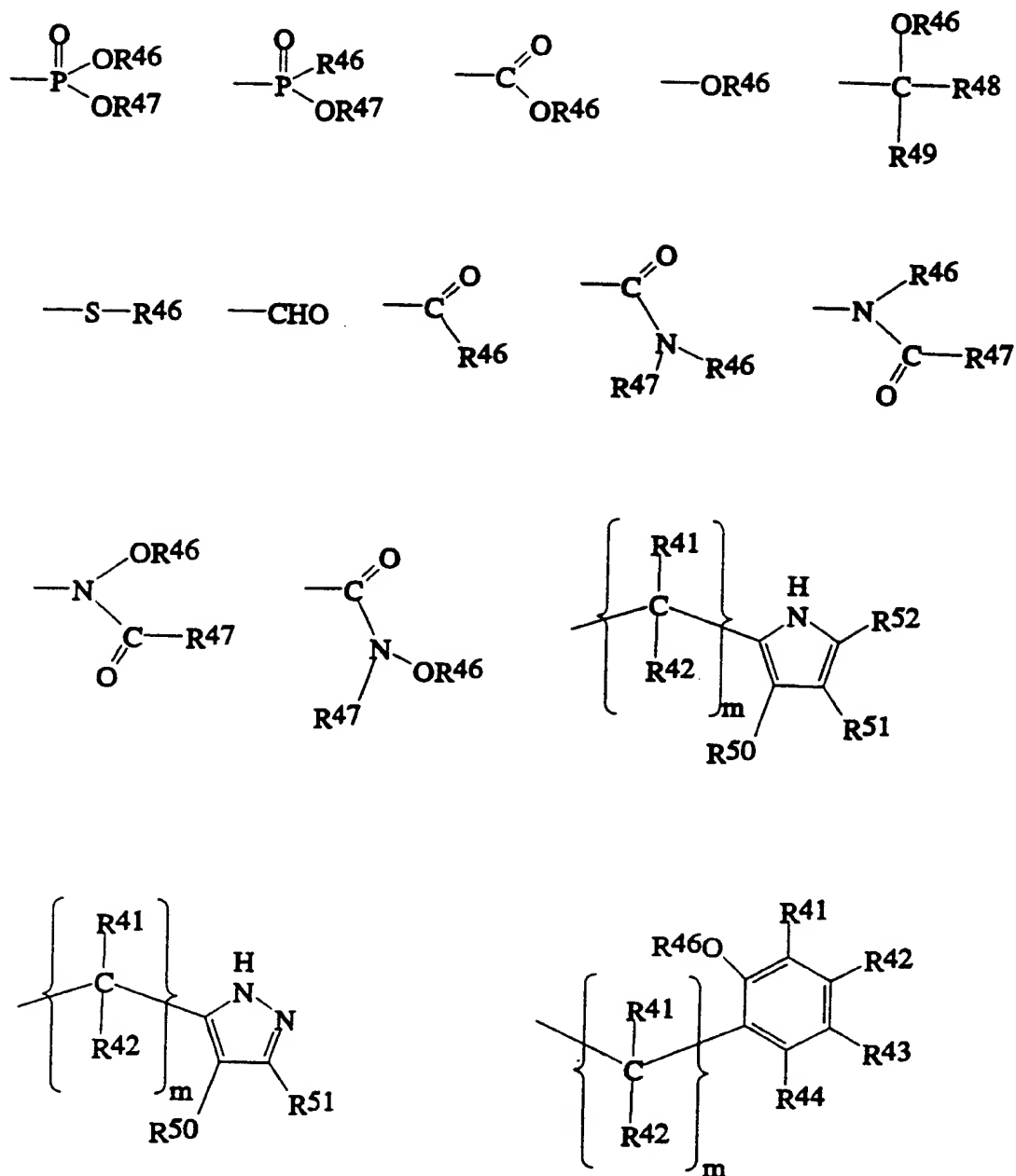
wherein,

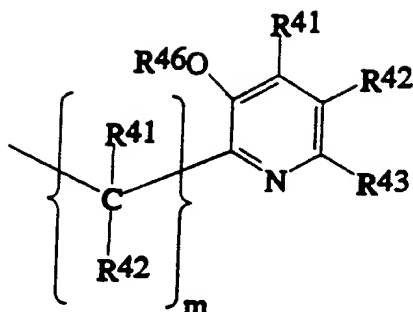
**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

**R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;**

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

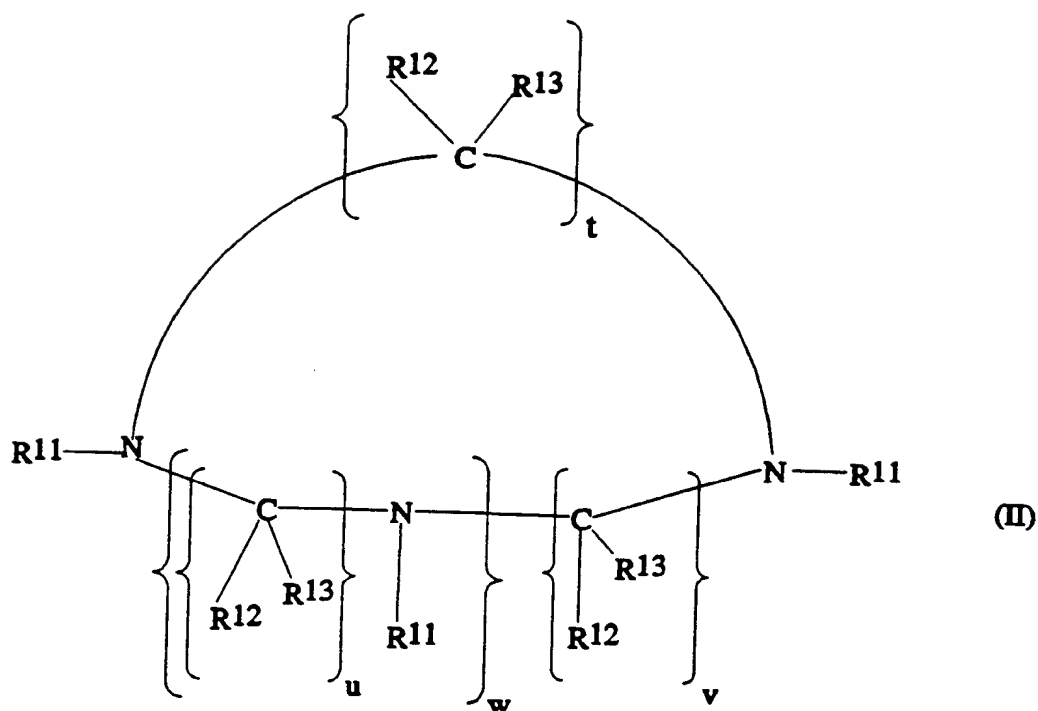
m is an integer of from 1 to 3,

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said compound does not exceed 2000; and a pharmaceutically acceptable carrier.

48. Compounds of the formula:

175



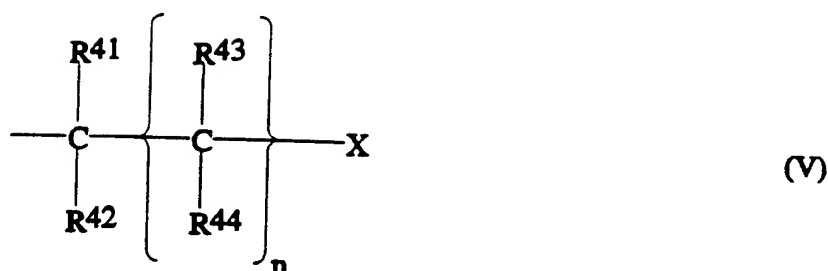
wherein,

**t, u and v are each independently 2 or 3;**

w is an integer of from 1 to 4;

**R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;**

**R<sup>11</sup> is a member selected from the group consisting of R<sup>12</sup>, R<sup>13</sup> and radicals of formula:**



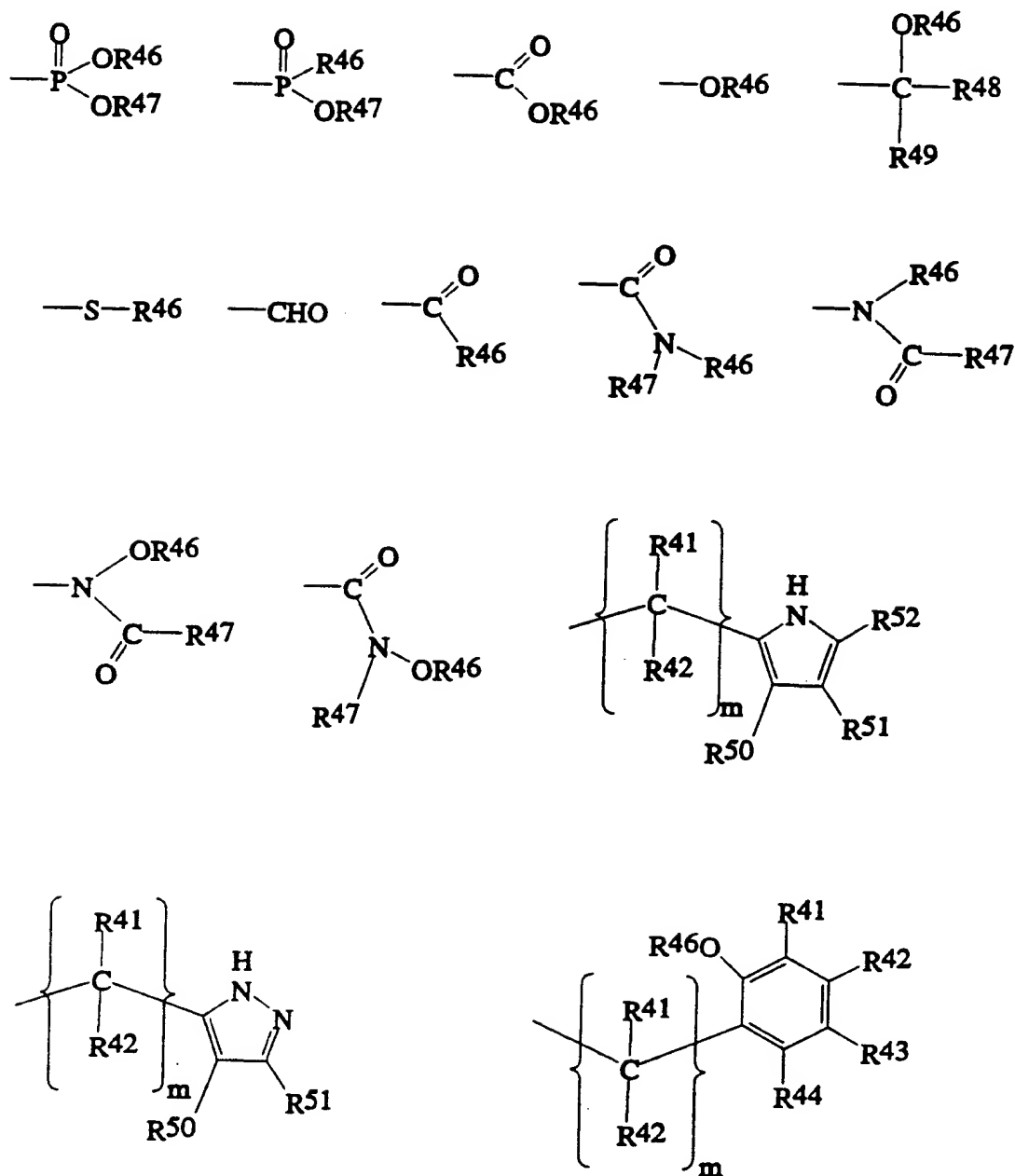
wherein,

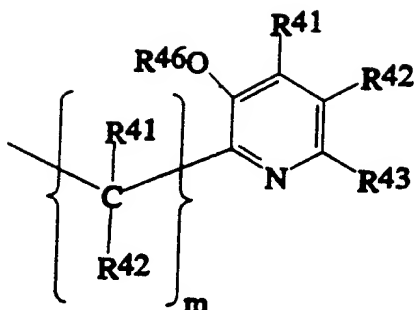
$\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

$\text{R}^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$n$  is zero or 1; and

$\text{X}$  is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein at least two of said R<sup>11</sup> groups comprise at least two contiguous carbon atoms directly attached to nitrogen atoms and the carbon atom in a position  $\beta$  to the nitrogen atom is substituted with a hydroxy and at least one member selected from the group consisting of hydroxymethyl, alkoxymethyl, alkenoxymethyl, aryloxymethyl and combinations thereof;

and wherein, optionally, any two of R<sup>11</sup>, R<sup>12</sup>, and R<sup>13</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of

said compound does not exceed 2000.

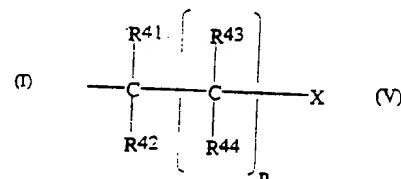
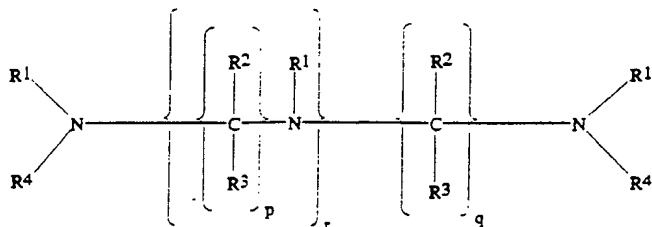
49. A compound in accordance with claim 48, wherein the cation of said physiological salts is sodium or N-methyl glucamine.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 49/00, 49/04, 51/00, 31/13, 31/28, A01N 33/02, 43/48, 43/64, 43/713, A61B 5/055, 5/05</b>		<b>A3</b>	(11) International Publication Number: <b>WO 97/01360</b>
			(43) International Publication Date: 16 January 1997 (16.01.97)
(21) International Application Number: <b>PCT/US96/10785</b>		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: <b>24 June 1996 (24.06.96)</b>			
(30) Priority Data: 60/000,524                      26 June 1995 (26.06.95)                      US 08/560,626                      20 November 1995 (20.11.95)                      US			
(71) Applicant (for all designated States except US): <b>CONCAT, LTD. [US/US]; Suite 101, 3205 Northwood Drive, Concord, CA 94520 (US).</b>			
(72) Inventors; and (75) Inventors/Applicants (for US only): <b>WINCHELL, Harry, S. [-/US]; 1 Via Oneg, Lafayette, CA 94549 (US). KLEIN, Joseph, Y. [-/IL]; 19 Naamat Street, 34670 Haifa (IL). SIMHON, Elliot, D. [-/IL]; 10 Klebanov Street, 32804 Haifa (IL). CYJON, Rosa, L. [-/IL]; 27 Burla Street, 32812 Haifa (IL). KLEIN, Ofer [-/IL]; 4 Mivtza Yehonatan Street, 34678 Haifa (IL). ZAKLAD, Haim [-/IL]; 22 Italia Street, 32812 Haifa (IL).</b>			
(74) Agents: <b>HEINES, M., Henry et al.; Townsend and Townsend and Crew L.L.P., Two Embarcadero Center, San Francisco, CA 94111-3834 (US).</b>		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
		(88) Date of publication of the international search report: 13 March 1997 (13.03.97)	

(54) Title: COMPOUNDS WITH CHELATION AFFINITY AND SELECTIVITY FOR FIRST TRANSITION SERIES ELEMENTS, AND THEIR USE IN MEDICAL THERAPY AND DIAGNOSIS



## (57) Abstract

This invention involves synthesis and use of a class of compounds having formula (I) wherein: p and q are each independently integers of from 2 to 3; r is an integer of from 0 to 4; R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof; R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula (V) and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms; and physiological salts thereof with the proviso that the molecular weight of said complexing agent does not exceed 2000, which chelation affinity and selectivity for first transition series elements. Administration of the free or conjugated compound, or physiological salts of the free or conjugated compound, results in decrease in the *in vivo* bioavailability of first transition series elements and/or removal from the body of first transition series elements and elements with similar chemical properties. These characteristics make such compounds useful in the management of diseases associated with a bodily excess of first transition series elements and elements with similar chemical properties. This invention demonstrates that such compounds inhibit mammalian, bacterial, and fungal cell replication and are therefore useful in the treatment of neoplasia, infection, inflammation, immune response, and in termination of pregnancy. Since these compounds are capable of decreasing the *in vivo* availability of tissue iron they are useful in management of free radical mediated tissue damage, and oxidation mediated tissue damage. When combined with radioisotopic or paramagnetic cations of first transition series elements, or elements with chemical properties similar to those of first transition series elements, prior to their administration, the resulting complexes are useful as diagnostic agents in nuclear medicine and magnetic resonance imaging (MRI).

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

# INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/US 96/10785

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K49/00 A61K49/04 A61K51/00 A61K31/13 A61K31/28  
A01N33/02 A01N43/48 A01N43/64 A01N43/713 A61B5/055  
A61B5/05

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 919 177 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 20 February 1963 see the whole document ---	1,3,9,21
X	GB 923 311 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 10 April 1963 see claims 1-10,12 ---	1-3,9,21
X	US 3 398 196 A (MILLER E.J. JR. & MAIS A.) 20 August 1968 see the whole document ---	1,3
X	US 3 432 547 A (GUTTMANN A.T. ET AL.) 11 March 1969 see the whole document ---	1-3,9
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 October 1996

Date of mailing of the international search report

- 4 -02- 1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

HARTRAMPF G.W.

# INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 96/10785

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 13 208 A (TH. GOLDSCHMIDT AG) 28 September 1972 see the whole document ---	1,3
X	GB 1 300 694 A (TH. GOLDSCHMIDT A.G.) 20 December 1972 see the whole document ---	1,3
X	DE 22 62 333 A (TH. GOLDSCHMIDT AG) 11 July 1974 see the whole document ---	1,3
X	US 3 906 105 A (MATT J. & SLOVINSKY M.) 16 September 1975 see the whole document ---	1,3
X	US 3 956 502 A (SLOVINSKY M. & MATT J.) 11 May 1976 see claims 1-3,6-9,12; table I ---	1,3
X	US 4 022 833 A (DIANA G.D. & CUTLER A.R.) 10 May 1977 see examples 35-47, 57 and 58 see column 4, line 38 - line 57; claim 1 ---	1-3,21
X	US 4 072 741 A (HUNSUCKER J.H.) 7 February 1978 see the whole document ---	1,3
X	GB 1 504 390 A (TH. GOLDSCHMIDT A.G.) 22 March 1978 see claims 1-4,12-15 ---	1,3
X	GB 1 513 671 A (L'OREAL) 7 June 1978 see the whole document ---	1-3,9,10
X	EP 0 309 980 A (THE B.F. GOODRICH COMPANY) 5 April 1989 see page 2, line 6; claims 6,7; examples 1-3 ---	1,3
A	FR 2 341 314 A (GOUPIL J.-J.) 16 September 1977  see page 2, line 15 - line 21 see page 3, line 21 - line 38 see page 4, line 27 - line 38 see page 5, line 23 - line 38 see page 6, line 26 - page 7, line 4 see page 8, line 1 - line 15 see page 11, line 32 - line 35 see page 18, line 1 - line 16; claims 1-4 --- -/--	1-5,9, 10,12, 21,22

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/10785

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 24444 A (BRITISH TECHNOLOGY GROUP LTD.) 9 December 1993 see the whole document ---	1,3
A	EP 0 258 616 A (SALUTAR, INC.) 9 March 1988 see claims 1-3,17-19,28,29 ---	20,46
A	WO 89 01476 A (CELLTECH LIMITED) 23 February 1989 see the whole document ---	20,46
A	FR 2 098 M (SOCIATA ANONYME DES LABORATOIRES ROBERT ET CARRIÈRE) 21 October 1963 see page 1, column 1, paragraph 3 ---	22
A	US 3 271 383 A (YAMAYA W. & MATSUI K.) 6 September 1966 see example 3; table 1 ---	22
A	GB 1 180 210 A (VEB FAHLBERG-LIST CHEMISCHE UND PHARMAZEUTISCHE FABRIKEN) 4 February 1970 see claim 1 ---	21,22
A	DE 22 60 444 A (C.H. BOEHRINGER SOHN) 12 June 1974 see claims 1,4-7; examples 1-6 ---	21,22
A	DE 23 00 543 A (BASF AG) 11 July 1974 see examples 29-32, 56, 57, 82-84, 109 and 110 see claims 1-10 ---	21,22
A	CH 599 924 A (C.H. BOEHRINGER SOHN) 15 June 1978 see the whole document -----	22

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 10785

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- |                          |                                 |
|--------------------------|---------------------------------|
| 1. Claims 1-3 (part.)    | 2. Claims 1-3 (part.) and 24-26 |
| 3. Claims 4-19 and 27-45 | 4. Claims 20 and 46             |
| 5. Claim 21              | 6. Claims 22, 23, 48 and 49     |

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-919177		NONE	
GB-A-923311		NONE	
US-A-3398196	20-08-68	DE-A- 1493443	06-11-69
		FR-A- 1462117	22-02-67
		GB-A- 1135048	
		GB-A- 1135050	
		SE-B- 333739	29-03-71
US-A-3432547	11-03-69	NONE	
DE-A-2113208	28-09-72	NONE	
GB-A-1300694	20-12-72	AT-A- 303269	15-10-72
		BE-A- 761318	16-06-71
		CH-A- 534480	15-03-73
		DE-A- 2009276	13-05-71
		FR-A- 2080797	19-11-71
		NL-A,B 7100500	31-08-71
		SE-B- 362585	17-12-73
		US-A- 3912816	14-10-75
DE-A-2262333	11-07-74	AT-B- 327401	26-01-76
		BE-A- 806413	15-02-74
		CH-A- 592046	14-10-77
		FR-A- 2211449	19-07-74
		NL-A- 7317529	24-06-74
US-A-3906105	16-09-75	CA-A- 1042017	07-11-78
US-A-3956502	11-05-76	NONE	
US-A-4022833	10-05-77	US-A- 3928427	23-12-75
		US-A- 4085144	18-04-78
		US-A- 4119668	10-10-78
		US-A- 4140860	20-02-79
US-A-4072741	07-02-78	NONE	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1504390	22-03-78	DE-A- 2457257	10-06-76
		BE-A- 836285	01-04-76
		FR-A- 2293418	02-07-76
		NL-A- 7513889	09-06-76
-----			
GB-A-1513671	07-06-78	LU-A- 70095	13-04-76
		LU-A- 71848	05-01-77
		BE-A- 829082	14-11-75
		BE-A- 829083	14-11-75
		CA-A- 1074497	25-03-80
		CA-A- 1134865	02-11-82
		CH-A- 611635	15-06-79
		CH-A- 629177	15-04-82
		DE-A- 2521898	04-12-75
		DE-A- 2521899	04-12-75
		FR-A- 2333012	24-06-77
		FR-A- 2270851	12-12-75
		GB-A- 1508215	19-04-78
		NL-A- 7505669	18-11-75
		NL-A- 7505672	18-11-75
-----			
EP-A-309980	05-04-89	JP-A- 1163160	27-06-89
		US-A- 5189173	23-02-93
-----			
FR-A-2341314	16-09-77	BE-A- 850982	31-05-77
		CA-A- 1109471	22-09-81
		CH-A- 622514	15-04-81
		DE-A- 2706826	01-09-77
		GB-A- 1578471	05-11-80
		US-A- 4323550	06-04-82
-----			
WO-A-9324444	09-12-93	EP-A- 0650471	03-05-95
		GB-A, B 2267438	08-12-93
		JP-T- 7507294	10-08-95
		US-A- 5464873	07-11-95
		US-A- 5583261	10-12-96
-----			
EP-A-258616	09-03-88	US-A- 5039512	13-08-91
		AT-T- 138809	15-06-96
		AU-B- 608759	18-04-91

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-258616		AU-A- 7573587	11-02-88
		CA-A- 1321346	17-08-93
		DE-D- 3751829	11-07-96
		DE-T- 3751829	31-10-96
		DE-A- 3777727	30-04-92
		EP-A- 0463644	02-01-92
		ES-T- 2087938	01-08-96
		FI-C- 88677	28-06-93
		IE-B- 64108	12-07-95
		NO-C- 173767	02-02-94
		US-A- 5219553	15-06-93
		JP-A- 63119446	24-05-88
-----			
WO-A-8901476	23-02-89	AT-T- 136302	15-04-96
		AU-B- 629515	08-10-92
		AU-A- 2253388	09-03-89
		DE-D- 3855177	09-05-96
		DE-T- 3855177	02-10-96
		EP-A- 0328589	23-08-89
		JP-T- 2501141	19-04-90
-----			
FR-M-2098		NONE	
-----			
US-A-3271383	06-09-66	NONE	
-----			
GB-A-1180210	04-02-70	BE-A- 730691	01-09-69
		CH-A- 513110	30-09-71
		DE-A- 1901549	20-08-70
-----			
DE-A-2260444	12-06-74	AT-B- 323131	25-06-75
		AT-B- 323132	25-06-75
		AT-B- 325022	25-09-75
		AT-B- 325023	25-09-75
		AT-B- 326107	25-11-75
		AU-A- 5294473	12-09-74
		CH-A- 601182	30-06-78
		CH-A- 599924	15-06-78
		CH-A- 605630	13-10-78
		CH-A- 605633	13-10-78
		CH-A- 605634	13-10-78

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2260444		CH-A- 605631	13-10-78
		CH-A- 605632	13-10-78
		FR-A- 2175055	19-10-73
		GB-A- 1431341	07-04-76
		JP-C- 1194741	12-03-84
		JP-A- 48103532	25-12-73
		JP-B- 58025657	28-05-83
		NL-A- 7303097	10-09-73
		SE-B- 413402	27-05-80
		US-A- 3888898	10-06-75
		US-A- 3969512	13-07-76
		US-A- 3975539	17-08-76
DE-A-2300543	11-07-74	NONE	
CH-A-599924	15-06-78	DE-A- 2210620	20-09-73
		DE-A- 2260444	12-06-74
		AT-B- 323131	25-06-75
		AT-B- 323132	25-06-75
		AT-B- 325022	25-09-75
		AT-B- 323133	25-06-75
		AT-B- 325023	25-09-75
		AT-B- 323134	25-06-75
		AT-B- 326107	25-11-75
		AU-A- 5294473	12-09-74
		BE-A- 796356	06-09-73
		CH-A- 601182	30-06-78
		CH-A- 605630	13-10-78
		CH-A- 605633	13-10-78
		CH-A- 605634	13-10-78
		CH-A- 605631	13-10-78
		CH-A- 605632	13-10-78
		FR-A- 2175055	19-10-73
		GB-A- 1431341	07-04-76
		JP-C- 1194741	12-03-84
		JP-A- 48103532	25-12-73
		JP-B- 58025657	28-05-83
		NL-A- 7303097	10-09-73
		SE-B- 413402	27-05-80
		US-A- 3888898	10-06-75

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A-599924		US-A- 3969512	13-07-76
		US-A- 3975539	17-08-76
-----			



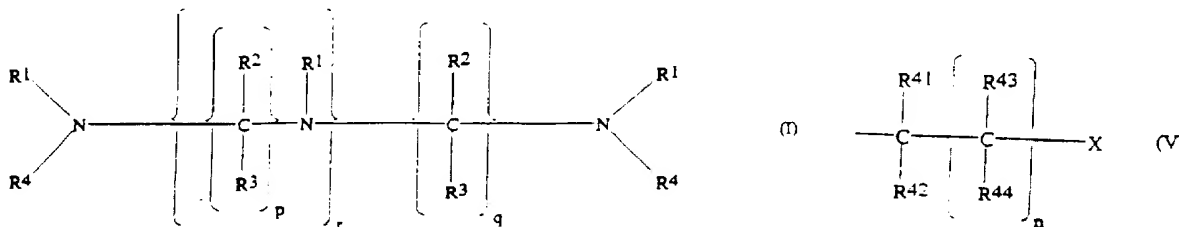
**PCT**

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 49/00, 49/04, 51/00, 31/13, 31/28, A01N 33/02, 43/48, 43/64, 43/713, A61B 5/055, 5/05</b>		<b>A3</b>	(11) International Publication Number: <b>WO 97/01360</b>
(21) International Application Number: PCT/US96/10785		(43) International Publication Date: 16 January 1997 (16.01.97)	
(22) International Filing Date: 24 June 1996 (24.06.96)		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 60/000,524 26 June 1995 (26.06.95) US 08/560,626 20 November 1995 (20.11.95) US		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant (for all designated States except US): CONCAT, LTD. [US/US]; Suite 101, 3205 Northwood Drive, Concord, CA 94520 (US).		(88) Date of publication of the international search report: 13 March 1997 (13.03.97)	
(72) Inventors; and (75) Inventors/Applicants (for US only): WINCHELL, Harry, S. [-/US]; 1 Via Oneg, Lafayette, CA 94549 (US). KLEIN, Joseph, Y. [-/IL]; 19 Naamat Street, 34670 Haifa (IL). SIMHON, Elliot, D. [-/IL]; 10 Klebanov Street, 32804 Haifa (IL). CYJON, Rosa, L. [-/IL]; 27 Burla Street, 32812 Haifa (IL). KLEIN, Ofer [-/IL]; 4 Mivtza Yehonatan Street, 34678 Haifa (IL). ZAKLAD, Haim [-/IL]; 22 Italia Street, 32812 Haifa (IL).			
(74) Agents: HEINES, M., Henry et al.; Townsend and Townsend and Crew L.L.P., Two Embarcadero Center, San Francisco, CA 94111-3834 (US).			

(54) Title: COMPOUNDS WITH CHELATION AFFINITY AND SELECTIVITY FOR FIRST TRANSITION SERIES ELEMENTS, AND THEIR USE IN MEDICAL THERAPY AND DIAGNOSIS



**(57) Abstract**

This invention involves synthesis and use of a class of compounds having formula (I) wherein: p and q are each independently integers of from 2 to 3; r is an integer of from 0 to 4; R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof; R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula (V) and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms; and physiological salts thereof with the proviso that the molecular weight of said complexing agent does not exceed 2000, which chelation affinity and selectivity for first transition series elements. Administration of the free or conjugated compound, or physiological salts of the free or conjugated compound, results in decrease in the *in vivo* bioavailability of first transition series elements and/or removal from the body of first transition series elements and elements with similar chemical properties. These characteristics make such compounds useful in the management of diseases associated with a bodily excess of first transition series elements and elements with similar chemical properties. This invention demonstrates that such compounds inhibit mammalian, bacterial, and fungal cell replication and are therefore useful in the treatment of neoplasia, infection, inflammation, immune response, and in termination of pregnancy. Since these compounds are capable of decreasing the *in vivo* availability of tissue iron they are useful in management of free radical mediated tissue damage, and oxidation mediated tissue damage. When combined with radioisotopic or paramagnetic cations of first transition series elements, or elements with chemical properties similar to those of first transition series elements, prior to their administration, the resulting complexes are useful as diagnostic agents in nuclear medicine and magnetic resonance imaging (MRI).

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<b>AM</b>	Armenia	<b>GB</b>	United Kingdom	<b>MW</b>	Malawi
<b>AT</b>	Austria	<b>GE</b>	Georgia	<b>MX</b>	Mexico
<b>AU</b>	Australia	<b>GN</b>	Guinea	<b>NE</b>	Niger
<b>BB</b>	Barbados	<b>GR</b>	Greece	<b>NL</b>	Netherlands
<b>BE</b>	Belgium	<b>HU</b>	Hungary	<b>NO</b>	Norway
<b>BF</b>	Burkina Faso	<b>IE</b>	Ireland	<b>NZ</b>	New Zealand
<b>BG</b>	Bulgaria	<b>IT</b>	Italy	<b>PL</b>	Poland
<b>BJ</b>	Benin	<b>JP</b>	Japan	<b>PT</b>	Portugal
<b>BR</b>	Brazil	<b>KE</b>	Kenya	<b>RO</b>	Romania
<b>BY</b>	Belarus	<b>KG</b>	Kyrgyzstan	<b>RU</b>	Russian Federation
<b>CA</b>	Canada	<b>KP</b>	Democratic People's Republic of Korea	<b>SD</b>	Sudan
<b>CF</b>	Central African Republic	<b>KR</b>	Republic of Korea	<b>SE</b>	Sweden
<b>CG</b>	Congo	<b>KZ</b>	Kazakhstan	<b>SG</b>	Singapore
<b>CH</b>	Switzerland	<b>LI</b>	Liechtenstein	<b>SI</b>	Slovenia
<b>CI</b>	Côte d'Ivoire	<b>LK</b>	Sri Lanka	<b>SK</b>	Slovakia
<b>CM</b>	Cameroon	<b>LR</b>	Liberia	<b>SN</b>	Senegal
<b>CN</b>	China	<b>LT</b>	Lithuania	<b>SZ</b>	Swaziland
<b>CS</b>	Czechoslovakia	<b>LU</b>	Luxembourg	<b>TD</b>	Chad
<b>CZ</b>	Czech Republic	<b>LV</b>	Latvia	<b>TG</b>	Togo
<b>DE</b>	Germany	<b>MC</b>	Monaco	<b>TJ</b>	Tajikistan
<b>DK</b>	Denmark	<b>MD</b>	Republic of Moldova	<b>TT</b>	Trinidad and Tobago
<b>EE</b>	Estonia	<b>MG</b>	Madagascar	<b>UA</b>	Ukraine
<b>ES</b>	Spain	<b>ML</b>	Mali	<b>UG</b>	Uganda
<b>FI</b>	Finland	<b>MN</b>	Mongolia	<b>US</b>	United States of America
<b>FR</b>	France	<b>MR</b>	Mauritania	<b>UZ</b>	Uzbekistan
<b>GA</b>	Gabon			<b>VN</b>	Viet Nam

**COMPOUNDS WITH CHELATION AFFINITY AND SELECTIVITY FOR FIRST TRANSITION SERIES ELEMENTS, AND THEIR USE IN MEDICAL THERAPY AND DIAGNOSIS.**

5

**CROSS REFERENCE TO RELATED APPLICATION**

This application is related to provisional application no.

10 60/000,524, filed June 26, 1995, and applications 08/543,425 and 08/405,562, each of which is incorporated by reference herein for all legal purposes to be served thereby.

The present invention lies in the field of metal cation chelators (ligands) and their use for purposes of decreasing the bioavailability of elements  
15 of the first transition series, and/or the removal from the body of these elements or those with similar chemical properties. First transition series elements are components of enzymes required for nucleic acid replication as well as general cell replication. By inhibiting nucleic acid replication these agents are useful in inhibiting growth of DNA and RNA viruses. By inhibiting  
20 bacterial and fungal cell replication these agents are useful *in vitro* as preservatives, and employing topical or systemic *in vivo* administration they are useful in treating bacterial and fungal infections and in wound care. By inhibiting protozoan cell replication these agents are useful in treatment of protozoan infections. By inhibiting mammalian cell replication, these agents are  
25 useful in treating neoplastic disease, in suppression of the immune response, in inhibition of osteoclast activity, and in termination of pregnancy. Iron, a first transition element, is involved in free radical mediated tissue damage. By decreasing the body free iron content, these agents inhibit free radical mediated tissue damage. Excess of body iron characterizes hemochromatosis/-  
30 hemosiderosis, and excess of the first transition series element, copper, characterizes Wilson's disease. By removing either excess iron or copper from the body these agents are useful in treating these diseases. When combined

with elements possessing paramagnetic properties, the chelating agents described herein also find diagnostic utility as contrast enhancing agents in magnetic resonance imaging. When combined with radioactive elements, these chelating agents find utility in nuclear medical imaging.

5

## BACKGROUND OF THE INVENTION

Metal cations belonging to the first transition series are known to play important coenzymatic roles in metabolism. Zinc is known to be a coenzyme for over eighty different enzyme systems including those directly involved with DNA and RNA synthesis such as thymidine kinase, DNA and RNA polymerases, reverse transcriptase and terminal deoxynucleotide transferase. Among its other coenzyme functions, iron is the coenzyme for myoglobin, the cytochromes and catalases and is thus essential for oxidative metabolism. Manganese and copper also play significant coenzyme roles, and other metal cations in the first transition series are considered to be essential trace elements although their metabolic role is less well defined.

Compounds capable of forming complexes with metal cations, which compounds are commonly referred to as chelators or ligands, are known to have a variety of uses in medicine. These include their use as pharmaceuticals in treating heavy metal poisoning, in treating diseases associated with trace metal excess such as iron storage and copper storage diseases (hemosiderosis and Wilson's disease, respectively), as radiopharmaceutical agents in nuclear medical imaging when forming complexes with radioactive metals, as contrast enhancement agents in magnetic resonance imaging (MRI) when forming complexes with paramagnetic metals, and as contrast enhancement agents in radiography when forming complexes with heavy metals.

Examples of ligands employed in treating heavy metal poisoning such as that due to lead, mercury, and other metals, are ethylenediamine tetraacetic acid (EDTA) and diethylenetriamine pentaacetic acid (DTPA). The ligand desferrioxamine is used in treating iron storage disease, and the ligand

penicillamine is used in the mobilization of copper in the treatment of Wilson's disease.

5 Examples of complexes used to form radiopharmaceuticals useful in evaluations of the kidneys, bone and liver are complexes of technetium-99m ( $^{99m}\text{Tc}$ ) with diethylenetriamine pentaacetic acid (DTPA), dimercaptosuccinic acid (DMSA), methylene diphosphonate (MDP) and derivatives of iminodiacetic acid (IDA).

10 Complexes of paramagnetic metal cations which are useful as MRI contrast agents operate by accelerating proton relaxation rates. Most commonly a metal cation, such as gadolinium (III), having a large number of unpaired electrons is complexed by a ligand suitable for complexation of that cation. An example is gadolinium (III) complexed by DTPA.

15 Chelators with affinity for iron cations have been shown to inhibit cell proliferation. Desferrioxamine is one example of such a chelator. This effect is thought to be a consequence of the complexation of tissue iron by the chelator, which thereby deprives the proliferating cells of a source of iron for critical enzyme synthesis. Moreover, it is believed that certain types of tissue damage are mediated by the formation of free radicals. It is also appreciated that catalytically active iron catalyzes formation of the highly active hydroxyl free radical. Based on such relationships chelators (ligands) for iron such as  
20 desferrioxamine and the experimental iron chelator "L1" (1,2-dimethyl-3-hydroxypyrid-4-one) have been examined in management of conditions where free radical mediated tissue damage is believed to play a role, as well as in clinical management of conditions in which control of cell  
25 proliferation is desired. Conditions where the administration of iron chelators has been evaluated include: rheumatoid arthritis, anthracycline cardiac poisoning, reperfusion injury, solid tumors, hematologic cancers, malaria, renal failure, Alzheimer's disease, myelofibrosis, multiple sclerosis, drug-induced lung injury, graft versus host disease, and transplant rejection and preservation  
30 (Voest, E.E., *et al.*, "Iron Chelating Agents in Non-Iron Overload conditions," *Annals of Internal Medicine* 120(6): 490-499 (15 March 1994)).

Agents which inhibit cell replication have found use in the prior art as chemotherapeutic agents for treatment of neoplasia and infectious disease,

for suppression of the immune response, and for termination of pregnancy. Such agents usually act by inhibiting DNA, RNA or protein synthesis. This results in a greater adverse effect on rapidly proliferating cell populations than on cells "resting" in interphase or proliferating less rapidly.

5           Such agents may possess a degree of selectivity in treating the rapidly proliferating offending cell population, particularly in the case of certain neoplasias and infectious processes. These agents also inhibit replication of normal cells of the host organism, to varying degrees. Cells of the immune system proliferating in response to antigenic challenge are sensitive to such  
10 agents, and accordingly these agents are useful in suppressing the immunological response. Examples are the suppression of the homograft rejection response following tissue transplantation and the treatment of autoimmune disorders. Replication of protozoan, bacterial and mycotic microorganisms are also sensitive to such agents, which makes the agents  
15 useful in treating infections by such microorganisms.

          Agents which suppress cell replication by inhibiting DNA or RNA synthesis have primarily found utility in treatment of neoplastic diseases. The glutamine antagonists azaserine, DON, and the anti-purines such as  
20 6-mercaptopurine and 6-thioguanine principally inhibit DNA synthesis by their action on phosphoribosylpyrophosphate amidotransferase, the enzyme involved in the first step in purine nucleotide synthesis. The folic acid antagonists aminopterin and methotrexate inhibit DNA synthesis (and other synthetic processes involving one carbon transport) by inhibiting the dihydrofolate reductase enzyme system, thereby interfering with formation of  
25 tetrahydrofolate, which is necessary in transfer of one-carbon fragments to purine and pyrimidine rings. Hydroxyurea inhibits DNA synthesis by inhibiting ribonuclease reductase, thereby preventing reduction of ribonucleotides to their corresponding deoxyribonucleotides. The anti-pyrimidines such as  
30 5-fluorouracil inhibit DNA synthesis by inhibiting thymidylate synthetase. 5-Fluorouracil may also be incorporated into fraudulent RNA molecules. Bleomycin appears to inhibit DNA synthesis by blocking thymidine incorporation into DNA, although it may have other mechanisms of action. Agents such as 5-bromouracil and iododeoxyuridine may be incorporated into DNA in place of

thymidine, and cytosine arabinoside may be incorporated into DNA in place of 2'-deoxycytidine. The fraudulent DNA produced by these incorporations interferes with the information transmittal system for DNA→RNA→protein synthesis.

5 Alkylating agents used in treating neoplasias, such as the nitrogen mustards, ethylene imines, alkyl sulphonates and antibiotics such as mitomycin C, suppress cell replication by attacking DNA and forming covalent alkylate linkages within preformed DNA, thereby interfering with DNA function and replication. The activity of such agents is therefore not limited to inhibition of  
10 cell replication alone.

Agents used in treatment of neoplasias such as 8-azaguanidine and 5-fluorouracil inhibit cell replication by being incorporated into fraudulent RNA. Agents such as actinomycin D, daunorubicin, nogalomycin, mithramycin and adriamycin are thought to inhibit RNA polymerase by strongly binding to  
15 DNA and thereby inhibiting DNA to RNA transcription.

Certain agents which inhibit cell replication by arresting metaphase (examples of such agents are colchicine, vinblastine, vincristine, podophyllotoxin, and griseofulvin) or arresting telophase (cytochalasins) have also been shown to be active in treating neoplasias or microbial infections.

20 Agents which inhibit cell replication primarily by inhibition of protein synthesis have found utility in the treatment of microbial infections. The tetracyclines, streptomycins and neomycin, for example, inhibit protein synthesis by inhibition of the mRNA-ribosome-tRNA complex. Chloramphenicol, erythromycin, lincomycin, puromycin appear to inhibit protein  
25 synthesis by inhibition of the peptidyl synthetase reaction. A miscellaneous group of antibiotics appear to act by inhibition of translocation of the ribosome along mRNA. Penicillins act by inhibiting synthesis of the bacterial cell wall.

Complexes of heavy metals such as platinum have been found to be active in treatment of certain neoplasias. The inhibition of cell replication by  
30 these complexes is attributed to the *in vivo* hydrolysis of one or more of the coordinating ligand sites occupying positions in the coordination shell of the metal. This hydrolysis liberates the coordination sites for *in vivo* interaction with nucleophilic donor sites which are critical to replication or survival of the

cell population. There is a wide diversity of such donor sites *in vivo*, but it is believed that one critical set of donor sites involves binding of the platinum to two guanine or one guanine and one adenine residue of opposing strands of DNA.

5           The mechanisms of action of the various agents employed in treating protozoan infection are largely unknown. However, it has been demonstrated that agents which interfere with cell replication can be active in treating such infections. For example, the antimalarial agent chloroguanide and the diaminopyrimidines act as selective inhibitors of plasmodial dihydrofolate  
10           reductase thereby inhibiting plasmodial DNA replication. Tetracyclines possess antimalarial and antiprotozoal activities possibly acting by mechanisms similar to those operative in their inhibition of bacterial replication. The antibiotics puromycin and erythromycin, as well as tetracyclines which inhibit microbial replication, have also been employed in treatment of amebiasis. The  
15           antiprotozoal effects of the diamidines is believed to be due to their inhibition of cell replication by interference with DNA.

          Based on what is known from the action of the agents cited above, one can readily conclude that agents which inhibit cell replication, regardless of the specific biochemical mechanism involved, have utility in the  
20           treatment of a wide variety of neoplastic and infectious diseases and in the management of certain of the body's responses which are mediated through selective *in vivo* cell replication.

#### SUMMARY OF THE INVENTION

25           The present invention resides in the discovery that a class of substituted polyaza compounds showing affinity and selectivity for first transition series elements (atomic numbers 21-30) are capable of inhibiting cell proliferation of mammalian, bacterial and yeast (fungal) cell populations and are therefore useful *in vitro* as preservatives and *in vivo*, administered topically or  
30           parenterally, in treatment of a wide variety of conditions including neoplasia, infection, inflammation, wound care, suppression of the immune response, inhibition of osteoclasts in treatment of osteoporosis and in termination of pregnancy. It is believed that the mechanism for inhibition of cell proliferation

by these compounds lies in their ability to decrease the bioavailability of essential first transition series elements. The term "decrease the bioavailability" is used herein to denote a reduction or elimination of the accessibility of these elements to biological systems and thereby a reduction or elimination of the ability of these elements to perform the functions they would otherwise perform in living systems. Since these compounds decrease the bioavailability of zinc and iron, they are useful in inhibiting replication of DNA and RNA viruses. Since these compounds decrease the *in vivo* availability of tissue iron, they are also useful in management of free radical-mediated tissue damage and oxidation-mediated tissue damage. The compounds can also be prepared as complexes with radioisotopic or paramagnetic cations of first transition series elements, or with elements having chemical properties similar to those of first transition series elements. Complexes prepared in this manner are useful as diagnostic agents in nuclear medicine and magnetic resonance imaging.

By virtue of their affinity and selectivity, these substituted polyaza compounds are effective in treating diseases characterized by excess of first transition series elements, such as hemosiderosis (iron) and Wilson's disease (copper).

For therapeutic purposes these agents may be employed in their free ligand form or in a protected form (for example, as the ester of the pendant donor group) where the protecting group can be removed *in vivo* by enzymatic action to release the active ligand form. The agents can be administered as either the free chelator, as a protected form of the chelator, or as physiological salts of these forms. Physiologically and pharmacologically acceptable salts of these compounds dissolved in suitable vehicles are fully suitable for use as pharmaceutical agents.

These compounds of this invention are chemically distinct from previously known antibiotic and chemotherapeutic agents which affect cell proliferation and which might also possess some properties as metal ion ligands. Unlike the chemotherapeutic complexes between a ligand and a heavy metal cation (such as platinum, for example) in which the complexed heavy metal provides the basis for the therapeutic effect and the purpose of the

ligand portion of the complex is related to the *in vivo* distribution and hydrolysis rates of the complex, the compounds of this invention are active in the form of the metal-free ligand and do not require the addition of a heavy metal to exercise their therapeutic effect. The compounds of the invention are also

5 chemically distinct from agents previously employed clinically as chelators of certain first transition series elements (such as desferrioxamine and 1,2-dimethyl-3-hydroxypyrid-4-one for chelation of iron, and penicillamine for chelation of copper).

Subclasses of compounds of this invention are novel compounds,

10 structurally distinct from previously disclosed chelators and any complexes derived therefrom. Complexes of these subclasses in combination with radioisotopes or paramagnetic cations are particularly useful in diagnostic studies in nuclear medicine or in magnetic resonance imaging, respectively.

## 15 DETAILED DESCRIPTION OF THE INVENTION

### Abbreviations

Abbreviations are used herein, in conformance with standard chemical practice, as follows: Bz, benzyl; Me, methyl; Et, ethyl; Pr, propyl; <sup>i</sup>Pr, isopropyl; <sup>i</sup>Bu, isobutyl; Bu, butyl; <sup>t</sup>Bu, *tertiary*-butyl; Ts, *para*-toluenesulfonyl; Tf<sup>-</sup>, trifluoroacetate; DMSO, dimethylsulfoxide; DMF, dimethylformamide; DEK, diethyl ketone (3-pentanone); MeOH, methanol; LDA, lithium diisopropylamide; THF, tetrahydrofuran; Py, pyridine; Ac, acetyl; Ac<sub>2</sub>O, acetic anhydride

20

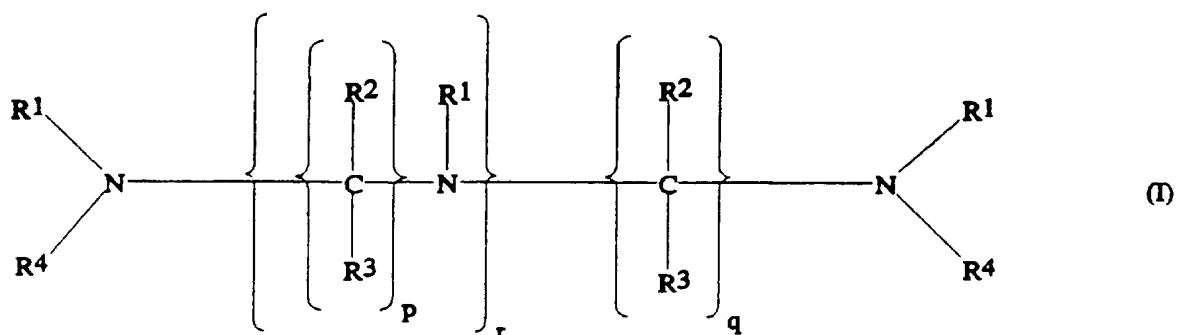
### 25 Embodiments of the Invention

The present invention provides methods of *in vitro* and *in vivo* complexing of first transition series element cations. The invention further provides methods of treating conditions dependent on the bioavailability of first transition series elements and also conditions associated with elevated levels of

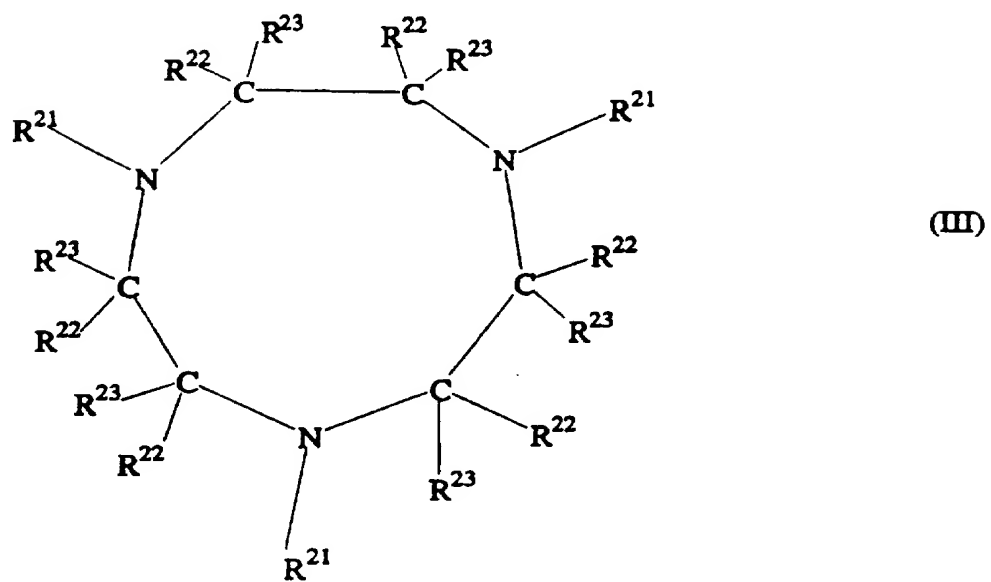
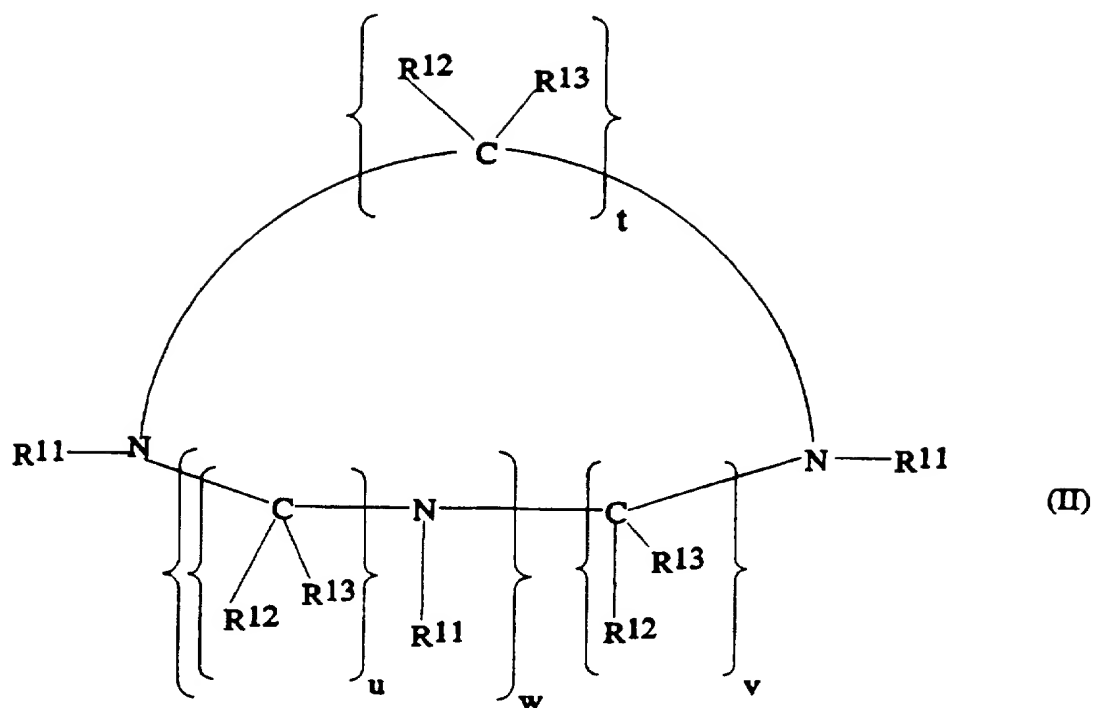
30 first transition series elements. Diagnostic methods are also provided which are useful in nuclear medicine and magnetic resonance imaging. The *in vivo* methods involve administering to a patient or host, a chelating agent (or ligand) which is capable of complexing first transition series elements as well as

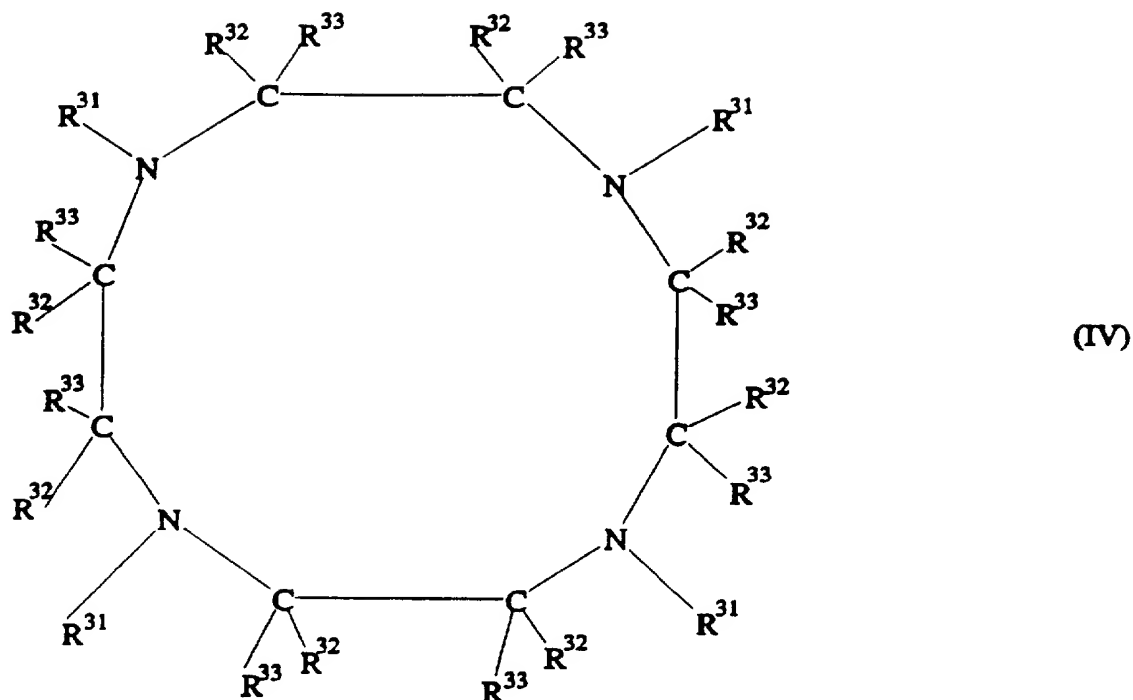
elements with chemical characteristics similar to those of first transition series elements. For the diagnostic methods, the chelating agent is administered as a complex of radioisotopic or paramagnetic cations of first transition series elements (or those with similar properties).

- 5 Among the ligands used in the practice of the present invention are the embodiments represented by the following formulas:



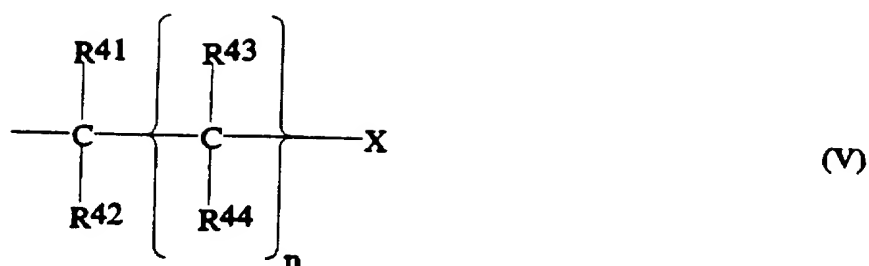
10





In Formulas I through IV,  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  may be the same or different on any single molecule, and the same is true for  $R^{11}$ ,  $R^{12}$ , and  $R^{13}$ , for  $R^{21}$ ,  $R^{22}$ , and  $R^{23}$ , and for  $R^{31}$ ,  $R^{32}$ , and  $R^{33}$ . Each of these symbols ( $R^1$  through  $R^{33}$ ) represents H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa (-O-), alkenyl interrupted by one or more oxa (-O-), alkyl interrupted by thia (-S-), alkenyl interrupted by thia (-S-), aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, or hydroxyarylalkyl, provided only that these groups do not interfere with complexation and they are not combined in a manner which results in a chemically unstable configuration. The alkyl, alkenyl and aryl groups, or portions of groups, in the foregoing list can also be substituted with one or more halogen atoms.

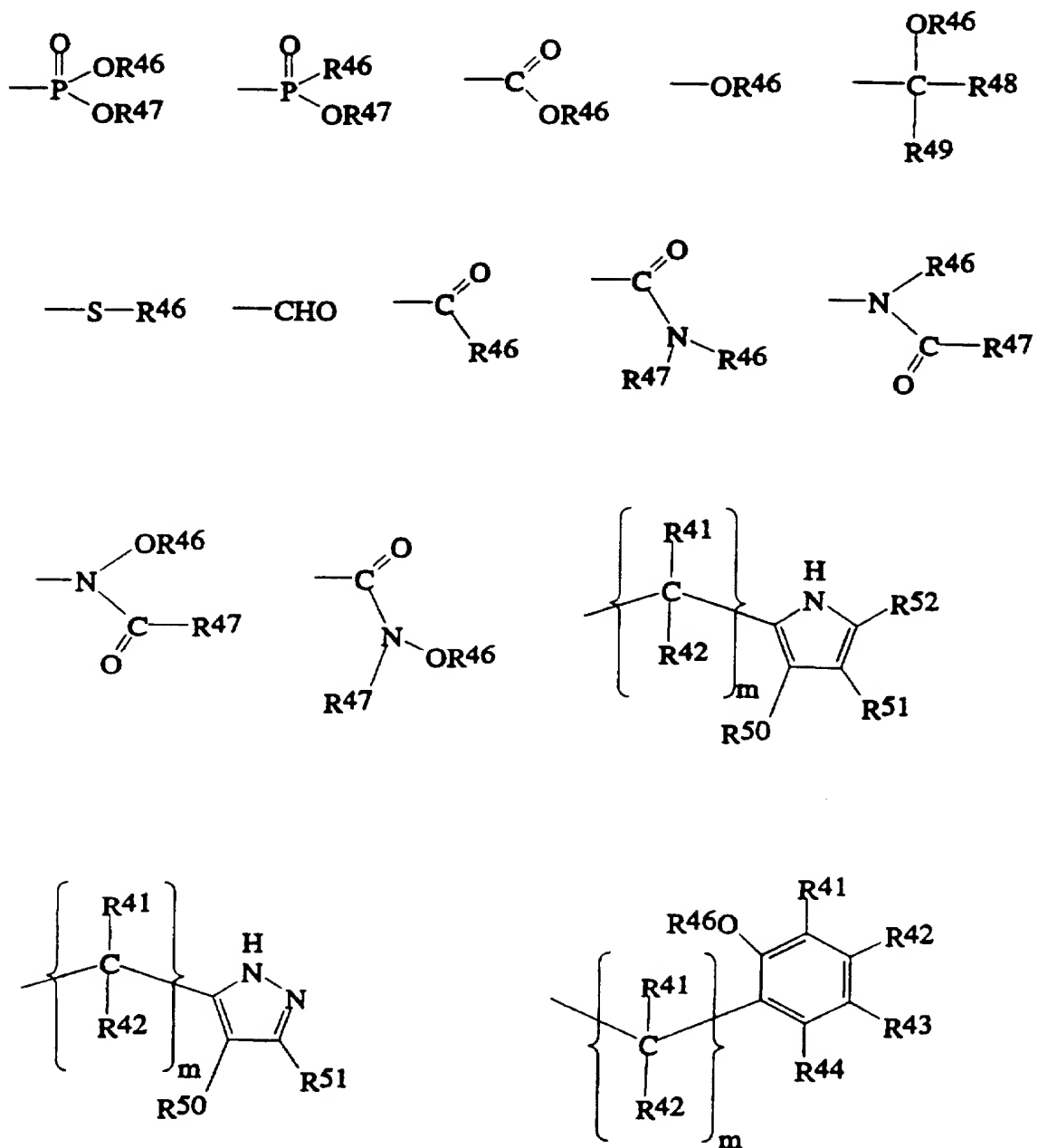
In addition to the radicals and radical subclasses listed above,  $R^1$ ,  $R^4$ ,  $R^{11}$ ,  $R^{21}$  and  $R^{31}$  are further defined to include:

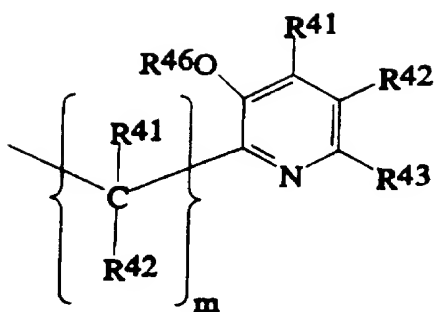


In Formula V,  $\text{R}^{41}$ ,  $\text{R}^{42}$ , and  $\text{R}^{43}$  may be the same or different on any single radical, and are defined as H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa (-O-), alkenyl interrupted by oxa (-O-), alkyl interrupted by thia (-S-), alkenyl interrupted by thia (-S-), aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, or hydroxyarylalkyl, provided only that these groups do not interfere with complexation and that they are not combined in a manner which results in a chemically unstable configuration. Here as well, the alkyl, alkenyl and aryl groups, or portions of groups, in the list can be substituted with one or more halogen atoms.  $\text{R}^{44}$  in Formula V is defined as H, hydroxy, amino, alkyl, alkyl interrupted by oxa (-O-), alkoxy, aryl, aryloxyalkyl, alkoxyaryl, or any of these groups in which the alkyl and aryl portions are substituted with one or more halogen atoms. Again, the groups are selected such that they do not interfere with complexation and are not combined in a manner which results in a chemically unstable configuration.

The index  $n$  is either zero or 1.

The symbol X represents any of the following groups:





In these formulas, R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup>, and R<sup>44</sup> may be the same or different on any single radical, and have the same definitions as R<sup>41</sup>, R<sup>42</sup>, and R<sup>43</sup> given above.

R<sup>46</sup>, R<sup>47</sup>, R<sup>48</sup> and R<sup>49</sup> may be the same or different on any single radical, and are each defined as H, or alkyl or aryl groups which do not interfere with complexation. R<sup>46</sup> and R<sup>47</sup> may further be combined as a single divalent group, thereby forming a ring structure. R<sup>48</sup> and R<sup>49</sup> are further defined to include alkoxy, alkyl interrupted by oxa (-O-), aryloxyalkyl, and alkoxyaryl, combined in a manner which results in a chemically stable configuration. All alkyl and aryl groups in this paragraph, including alkyl and aryl portions of groups, are optionally substituted with one or more halogen atoms.

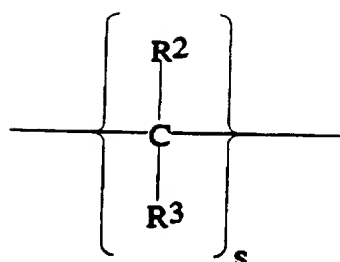
R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> may be the same or different on any single radical, and are each defined as H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, or hydroxyarylalkyl.

The index m is an integer which is either 1, 2 or 3.

Returning to Formulas I through IV, further variations within the scope of this invention are as follows:

(1) Internal cyclizations within these formulas at the nitrogen atoms, formed by joining together any two of the R<sup>1</sup> and R<sup>2</sup> groups in Formula I, any two of the R<sup>11</sup> groups in Formula II, any two of the R<sup>21</sup> groups in Formula III, or any two of the R<sup>31</sup> groups in Formula IV, as a single divalent group bridging the two nitrogen atoms, the single divalent group having the formula

15



(VI)

in which R<sup>2</sup> and R<sup>3</sup> are as defined above, and s is at least 2, preferably 2 or 3;

5

(2) Dimers or other two-molecule combinations of Formulas I through IV (the molecules being the same or different), formed by bridging the molecules together through one or more divalent groups of Formula VI (as defined above) substituted for any one or two of the R<sup>11</sup> groups in Formula II, any one or two of the R<sup>21</sup> groups in Formula III, or any one or two of the R<sup>31</sup> groups in Formula IV;

10

(3) Internal cyclizations at common carbon atoms within these formulas to form homocyclic rings, by joining one or more of the R<sup>2</sup>, R<sup>12</sup>, R<sup>22</sup>, or R<sup>32</sup> groups to one or more of the R<sup>3</sup>, R<sup>13</sup>, R<sup>23</sup>, or R<sup>33</sup> groups at the same carbon atom, as a single divalent group of Formula VI (as defined above), and forming one or more such homocyclic rings per structure in this manner; and

15

(4) Internal cyclizations involving two carbon atoms separated by a nitrogen atom within these formulas to form heterocyclic rings, by joining any two adjacent R<sup>2</sup> groups in Formula I, any two adjacent R<sup>12</sup> groups in Formula II, any two adjacent R<sup>22</sup> groups in Formula III, or any two adjacent R<sup>32</sup> groups in Formula IV, as a single divalent group of Formula VI (as defined above), and forming one or more such heterocyclic rings per structure in this manner.

20

In Formula I, the subscripts p and q may be the same or different, and are each either 2 or 3. The subscript r is 0 to 4 inclusive, preferably 1 to 2 inclusive.

25

In Formula II, t, u and v may be the same or different, and are each either 2 or 3. The value of w is at least 1, more preferably 1 to 4

inclusive, still more preferably 1 to 3 inclusive, and most preferably either 1 or 2.

The terms used in connection with these formulas have the same meaning here as they have in the chemical industry among those skilled in the art. The term "alkyl" thus encompasses both straight-chain and branched-chain groups and includes both linear and cyclic groups. The term "alkenyl" refers to unsaturated groups with one or more double bonds and includes both linear and cyclic groups. The term "aryl" refers to aromatic groups of one or more cycles.

For all such groups, those which are useful in the present invention are those which do not impair or interfere with the formation of chelate complexes. Within this limitation, however, the groups may vary widely in size and configuration. Preferred alkyl groups are those having 1 to 8 carbon atoms, with 1 to 4 carbon atoms more preferred. Prime examples are methyl, ethyl, isopropyl, *n*-butyl and *tert*-butyl. Preferred aryl groups are phenyl and naphthyl, particularly phenyl. Preferred aryl alkyl groups are phenylethyl and benzyl, and of these benzyl is the most preferred. Preferred cycloalkyl groups are those with 4 to 7 carbon atoms in the cycle, with cycles of 5 or 6 carbon atoms particularly preferred. Preferred halogen atoms are chlorine and fluorine, with fluorine particularly preferred.

One particularly preferred subclass of compounds within Formula I are those in which  $R^1$  is alkyl, alkenyl, aryl, arylalkyl, or cycloalkyl, substituted at the  $\beta$ -position with hydroxy. Likewise,  $R^{11}$  in Formula II,  $R^{21}$  in Formula III, and  $R^{31}$  in Formula IV are each preferably alkyl, alkenyl, aryl, arylalkyl, or cycloalkyl, substituted at the  $\beta$ -position with hydroxy. Further preferred are compounds in which one or more, and preferably two or more, of such groups ( $R^1$ ,  $R^{11}$ ,  $R^{21}$  and  $R^{31}$  on the same formula are substituted at the  $\beta$ -position with hydroxy. Still further preferred are compounds in which the  $\beta$ -hydroxy substituted groups are further substituted at the  $\beta$ -position with at least one hydroxymethyl, alkoxymethyl, alkenoxymethyl, aryloxymethyl, or combinations thereof, all of which may also be further substituted with halogen. Included among these are compounds of Formula III in which one or more of the  $R^{21}$  groups are substituted at the  $\beta$ -position with hydroxy and also with hydroxymethyl, alkoxymethyl, alkenoxymethyl, or aryloxymethyl, all of

which may also be further substituted with halogen, and the R<sup>22</sup> and R<sup>23</sup> groups are all hydrogen atoms.

Certain specific groups for R<sup>1</sup>, R<sup>11</sup>, R<sup>21</sup>, and R<sup>31</sup> are particularly preferred. These are: 2-hydroxy(2,2-diisopropoxymethyl)ethyl and  
5 (3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl.

For use in the present inventive methods, the complexes will preferably have a molecular weight which does not exceed 2000. More preferably the complexes will have molecular weights of from 200 to 1800, still more preferably of from 400 to 1100.

10 Among the complexes used in the practice of the present invention are the embodiments represented by the complexes formed between the ligands described above and paramagnetic metal cations or radioisotopic metal cations. These paramagnetic metal cations include elements of atomic numbers 22 through 29 (inclusive), 42, 44 and 58 through 70 (inclusive). Of  
15 these, the ones having atomic numbers 22 through 29 (inclusive) and 58 through 70 (inclusive) are preferred, and those having atomic numbers 24 through 29 (inclusive) and 64 through 68 (inclusive) are most preferred. Examples of such metals are chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium  
20 (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III). Chromium (III), manganese (II), iron (III) and gadolinium (III) are particularly preferred, with gadolinium (III) the most preferred.

Some methods of the present invention will use radioisotopic labels which will facilitate imaging of various disease states including tumors,  
25 inflamed joints or lesions or suspected lesions. The use of gamma emitting radioisotopes is particularly advantageous as they can easily be counted in a scintillation well counter, do not require tissue homogenization prior to counting, and can be imaged with gamma cameras.

Gamma or positron emitting radioisotopes are typically used in  
30 accordance with well known techniques. Suitable gamma-emitting radioisotopes include <sup>99</sup>Tc, <sup>51</sup>Cr, <sup>59</sup>Fe, <sup>67</sup>Ga, <sup>86</sup>Rb, <sup>111</sup>In and <sup>195</sup>Pt. Suitable positron-emitters include <sup>68</sup>Ga.

Where indicated, physiologically or pharmacologically compatible salts of the ligands, or complexes thereof, which have an excess of acidic groups are formed by neutralizing the acidic moieties of the ligand with physiologically or pharmacologically compatible cations from corresponding inorganic and organic bases and amino acids. Examples are alkali and alkaline earth metal cations, notably sodium. Further examples are primary, secondary and tertiary amines, notably, ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, and N-methylglucamine (commonly referred to as "meglumine"). Examples of amino acid cations are lysines, arginines and ornithines.

Similarly, physiologically and pharmacologically compatible salts of those ligands which have an excess of basic groups are formed by neutralizing the basic moieties of the ligand with physiologically or pharmacologically compatible anions from corresponding inorganic and organic acids. Examples are halide anions, notably chloride. Further examples are sulfates, bicarbonate, acetate, pyruvate and other inorganic and organic acids.

Pharmaceutical compositions comprising the chelates described herein are prepared and administered according to standard techniques. The pharmaceutical compositions can be administered parenterally, *i.e.*, intraarticularly, intravenously, subcutaneously, or intramuscularly. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed. (1985).

The chelate compositions can be administered intravenously. Thus, this invention provides compositions for intravenous administration which comprise a solution of the chelate suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, *e.g.*, water, buffered water, 0.9% isotonic saline, and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate

physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, *etc.*

5           The concentration of chelates, in the pharmaceutical formulations can vary widely, *i.e.*, from less than about 0.05%, usually at or at least about 2-5% to as much as 10 to 30% by weight and will be selected primarily by fluid volumes, viscosities, *etc.*, in accordance with the particular mode of administration selected. For diagnosis, the amount of chelates in administered  
10 complexes will depend upon the particular metal cation being used and the judgement of the clinician. For use in magnetic resonance imaging the dose typically is between 0.05 to 0.5 millimoles/kg body weight.

          In general, any conventional method for visualizing diagnostic imaging can be used, depending upon the label used. Usually gamma and  
15 positron emitting radioisotopes are used for imaging in nuclear medicine and paramagnetic metal cations are used in magnetic resonance imaging.

          The methods of the present invention may be practiced in a variety of hosts. Preferred hosts include mammalian species, such as humans, non-human primates, dogs, cats, cattle, horses, sheep, and the like.

20           The foregoing description and the following examples are offered primarily for illustration and not as limitations. It will be readily apparent to those of ordinary skill in the art that the operating conditions, materials, procedural steps and other parameters of the compositions and methods described herein may be further modified or substituted in various ways  
25 without departing from the spirit and scope of the invention.

## **EXAMPLES**

### **EXAMPLE 1**

30           This example illustrates the synthesis of chelators (ligands) which are useful in the present invention. Section 1.1 illustrates the synthesis of

polyaza bases. Section 1.2 illustrates the synthesis of alkylating groups. Section 1.3 illustrates the preparation of chelating agents from alkylation of polyaza bases.

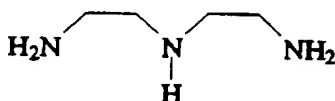
In all examples reactions were carried out in common solvents, compounds were purified by routine methodology and identity was established by proton NMR. In some cases identity was further verified by elemental analysis, mass spectroscopy, C-13 or P-31 NMR, or by synthesis of the identical compound by an independent alternate synthesis route.

### 1.1 SYNTHESIS OF POLYAZA BASES

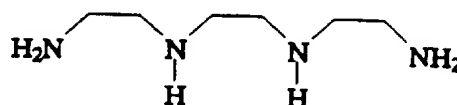
Ethylene diamine (1.1.0), diethylene triamine (1.1.1), triethylenetetramine (1.1.2), 1,4,7-triazacyclononane (1.1.3), 1,4,7,10-tetraazacyclododecane (1.1.4), 1,4,8,11-tetraazacyclotetradecane (1.1.5) & 1,5,9,13-tetraazacyclohexadecane (1.1.6) and the corresponding hydrohalide salts were either obtained from commercial sources or were synthesized employing established methods and were used directly in the syntheses of chelators (ligands) described in section 1.3. Additional polyaza bases were synthesized as described herein.



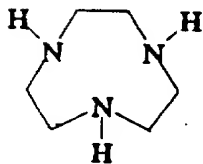
1.1.0



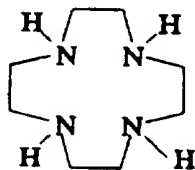
1.1.1



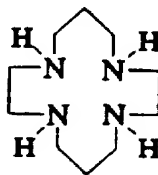
1.1.2



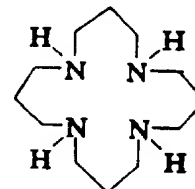
1.1.3



1.1.4



1.1.5



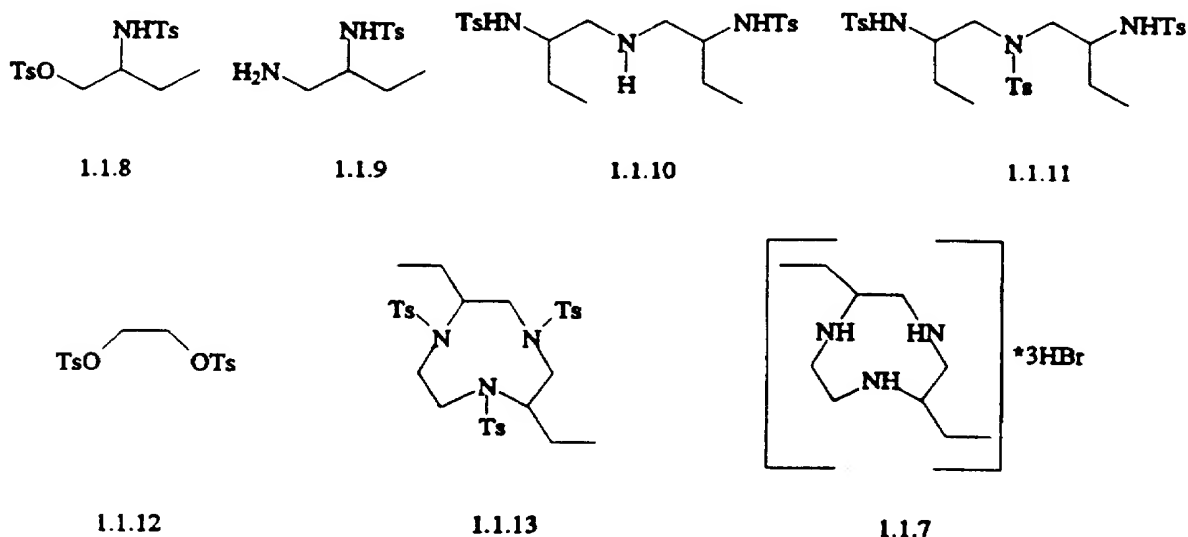
1.1.6

1.1.7 2,6-Diethyl-1,4,7-triazacyclononane trihydrobromide

2-(p-toluenesulfonylamino)-1-(p-toluenesulfonyloxy) butane (1.1.8) and ammonium hydroxide were reacted to form 2-(p-toluenesulfonamino)-1-

## 21

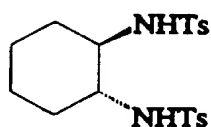
aminobutane (1.1.9). This was reacted with 2-(p-toluenesulfonylamino)-1-(p-toluenesulfonyloxy)butane (1.1.8) and potassium carbonate. The 3,7 bis(p-toluenesulfonylamino)-5-azanonane (1.1.10) product was purified by chromatography and reacted with p-toluenesulfonyl chloride to obtain the corresponding tri-p-toluenesulfonyl compound 3,7 bis(p-toluenesulfonylamino)-5-(p-toluenesulfonyl)-5-azanonane (1.1.11). This was purified by chromatography and reacted with 2.2 equivalents of sodium amide in DMF and then with 1,2-di(p-toluenesulfonyloxy)ethane (1.1.12). The 2,6-diethyl-1,4,7-tris(p-toluenesulfonyl) triazacyclononane (1.1.13) that was obtained following purification was heated in a solution of HBr in acetic acid to remove the p-toluenesulfonyl groups and form the titled compound (1.1.7)



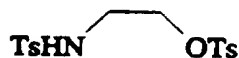
**1.1.14            1,4,7-Triazabicyclo[7.4.0<sup>8,13</sup>]tridecane trihydrobromide**

1,2-trans-bis(p-toluenesulfonylamino)cyclohexane (1.1.15) was treated with NaH in DMSO. 1-(p-toluenesulfonylamino)-2-(p-toluenesulfonyl) ethane (1.1.16) was added to obtain 1-(p-toluenesulfonylamino)-2-[N-p-toluenesulfonyl-N-(2-p-toluenesulfonylaminoethyl)] aminocyclohexane (1.1.17). This was separated and reacted with NaH and 1,2-di(p-toluenesulfonyloxy)ethane (1.1.12) was added. The 2,3-butano-N,N'N''-tris(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.1.18) obtained was purified by chromatography. The p-toluenesulfonyl groups were removed by reaction in

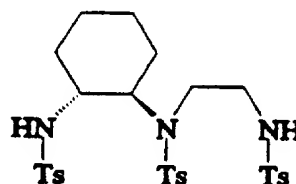
HBr/Acetic acid and the 2,3-butano-1,4,7-triazacyclononane trihydrobromide (1.1.14) product precipitated from solution as the hydrobromide salt.



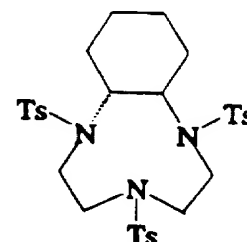
1.1.15



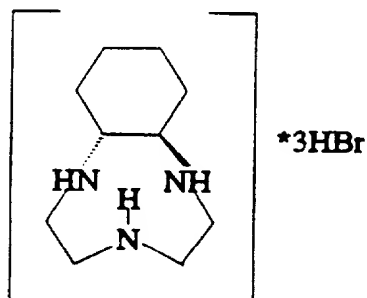
1.1.16



1.1.17



1.1.18



1.1.14

5

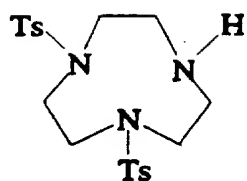
### 1.1.19 1,3-Bis (1,4,7-triazacyclononane) propane

N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.1.20) was prepared by reacting (1.1.3) with two equivalents of p-toluenesulfonyl chloride. Two equivalents of N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.1.20) hydrobromide were reacted with one equivalent of 1,3-diiodopropane in acetonitrile with excess potassium carbonate. 1,3-Bis[N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane] propane (1.1.21) was isolated and purified by chromatography. The p-toluenesulfonyl groups were removed using sulfuric acid and HBr to yield the title compound (1.1.19).

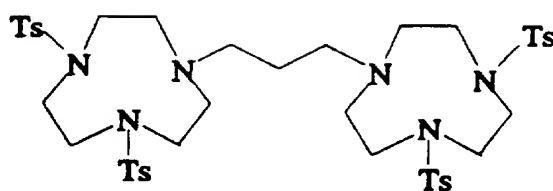
10

15

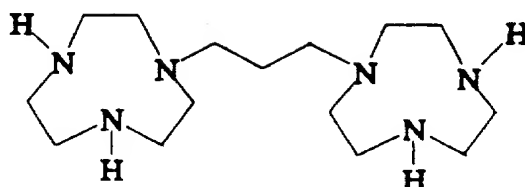
23



1.1.20



1.1.21

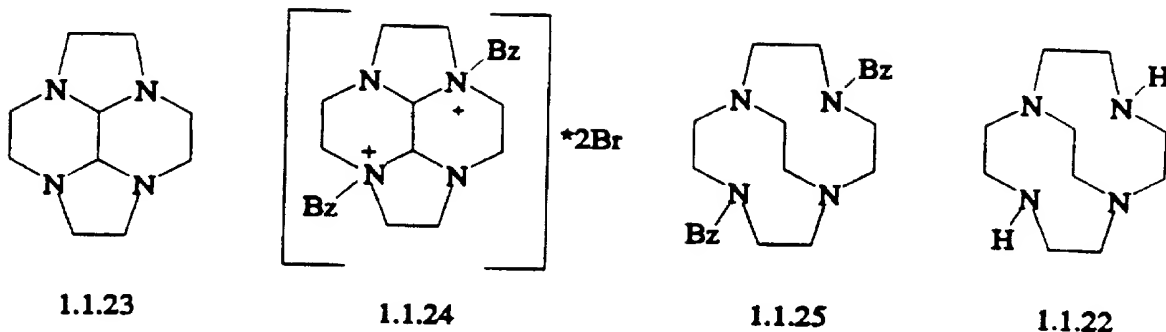


1.1.19

**1.1.22 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane**

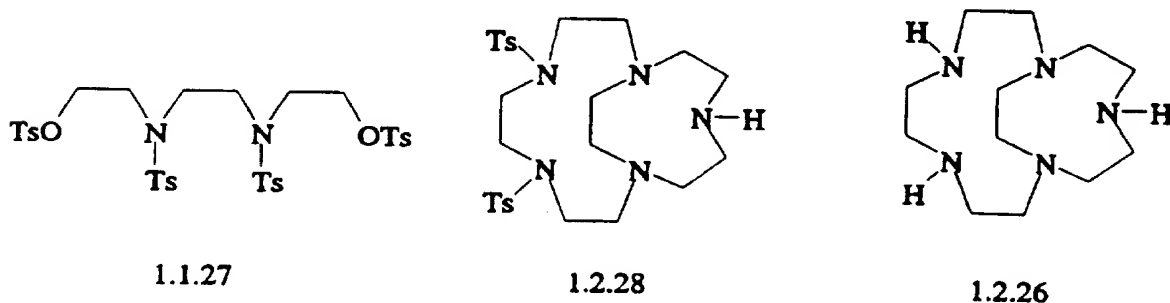
1,4,7,10-tetraazadodecane (1.1.4) trihydrobromide in acetonitrile

- 5 with potassium carbonate was reacted with glyoxal to form 1,4,7,10-tetraazatetracyclo-[5,5,2,0<sup>4,13</sup>,0<sup>10,14</sup>] tetradecane (1.1.23). Following separation the pure product was obtained by low pressure distillation. This was dissolved in acetonitrile and benzylbromide was added to form 1,7-dibenzylum-1,4,7,10-tetraazatetracyclo[5,5,2,0<sup>4,13</sup>,0<sup>10,14</sup>] tetradecane
- 10 (1.1.24). Following recrystallization from ethanol this was reacted with sodium borohydride. HCl was added, followed by water and NaOH, and the product extracted with chloroform. Following evaporation of solvent the solids were dissolved in methanol and HBr was added to obtain 1,7-dibenzyl-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane (1.1.25) as the hydrobromide salt. This
- 15 was dissolved in water and reduced using H<sub>2</sub> and a Pd-C catalyst to remove the benzyl groups. Purification of the title compound was by crystallization of the hydrobromide salt. The base form was obtained by low pressure distillation following addition of base.



**1.1.26      1,4,7,10,13-Pentaazabicyclo [8.5.2] heptadecane.**

5      To 1,8-bis(p-toluenesulfonyloxy)-3,6-bis(p-toluenesulfonyl)-3,6-diazaoctane(1.1.27) was added 1,4,7-triazacyclononane(1.1.3) in acetonitrile with potassium bicarbonate to obtain 4,7-bis (p-toluenesulfonyl)-1,4,7,10,13-pentaazabicyclo [8.5.2] (1.1.28) heptadecane. The title compound was purified and the p-toluenesulfonyl groups were removed by treatment in sulfuric acid. Purification was done by low pressure distillation.



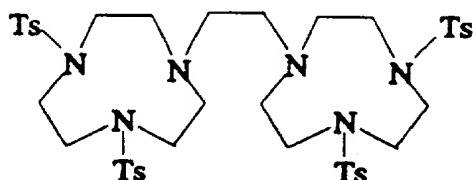
**1.1.29      1,2-Bis(1,4,7-triazabicyclononane-1-yl) ethane.**

15      A mixture of N,N'-bis(p-toluenesulfonyl)-1,4,7-triazabicyclonone hydrobromide (1.1.13.33), ethylene glycol di-p-toluenesulfonyl or dibromoethane and excess of potassium carbonate in acetonitrile was refluxed overnight. The reaction mixture was added to water and extracted with methylene chloride. The tetratosylated product (1.1.30) was purified by chromatography. It was suspended in 70% H<sub>2</sub>SO<sub>4</sub> and heated at 150°C for 15 hrs. The reactions cooled to room temperature and then 62% HBr solution was added. The white precipitate was collected and washed with ethanol. It was

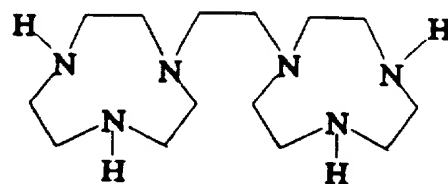
20

## 25

redissolved in water and filtered from tars. The water was made basic and the title compound (1.1.29) was extracted with chloroform.



1.1.30



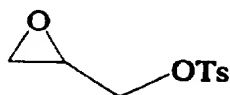
1.1.29

## 5 1.2 SYNTHESIS OF ALKYLATING GROUPS FOR ALKYLATION OF POLYAZA BASES TO FORM CHELATORS DESCRIBED IN EXAMPLE 1.3.

### 1.2.1 Preparation of Glycidyl Ethers

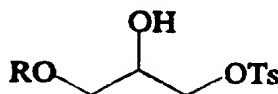
10 Glycidyl tosylate (R, S or d,l) (1.2.1.0) was reacted in the appropriate alcohol solvent employing catalytic amounts of conc.  $H_2SO_4$  or equivalent amounts of tetrafluoroboranetherate. The 1-alkyloxy-2-hydroxy-3-p-toluenesulfonyloxypropane (1.2.1.1) product was reacted in ether with BuLi to yield the title epoxide. The following compounds were prepared in this manner.

15 1.2.1.0 Glycidyl tosylate (R,S or d,l; commercially available).



1.2.1.0

1.2.1.1 1-Alkyloxy-2-hydroxy-3-p-toluenesulfonyloxypropane.

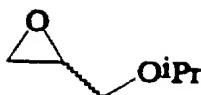


1.2.1.1

20

1.2.1.2 d,l-Glycidyl-isopropyl ether (commercially available).

26



1.2.1.2

1.2.1.3 (2R) Glycidyl-isopropyl ether.

5 1.2.1.4 (2S) Glycidyl-isopropyl ether.

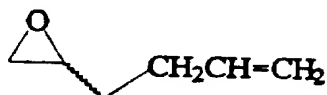
1.2.1.5 d,l-Glycidyl-t-butyl ether.



1.2.1.5

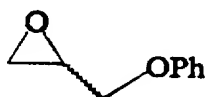
10 1.2.1.6 (2R) Glycidyl-t-butyl ether.

1.2.1.7 d,l-Glycidyl allyl ether.



1.2.1.7

15 1.2.1.8 d,l-Glycidyl phenyl ether

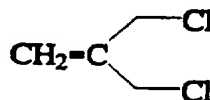


1.2.1.8

1.2.2 Preparation of 2,2-Dialkoxymethylene Oxiranes and Spiro-Oxiranes

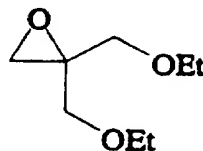
3-Chloro-2-chloromethyl-1-propane (1.2.2.0) was reacted with the corresponding sodium alkylate or disodium dialkylate either using the same alcohol or dialcohol as solvent or using an inert solvent. The ether product was purified by distillation or chromatography. Epoxidation was performed using *meta*-chloroperbenzoic acid in halogenated solvent. The following compounds were prepared in this manner.

1.2.2.0 3-Chloro-2-chloromethyl-1-propane (commercially available).



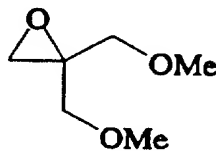
1.2.2.0

1.2.2.1. 2,2-Bis-ethoxymethyl oxirane.



1.2.2.1

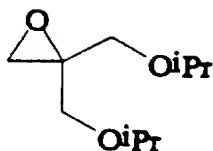
1.2.2.2 2,2-Bis-methoxymethyl oxirane.



1.2.2.2

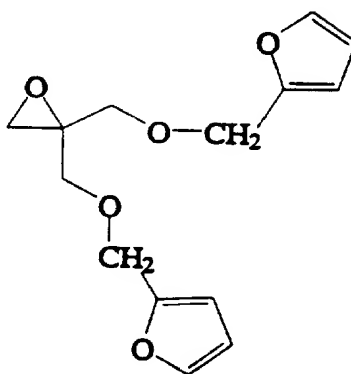
1.2.2.3 2,2-Bis-isopropyloxymethyl oxirane.

28



1.2.2.3

#### 1.2.2.4 2,2-Bis-difurfuryloxymethyl oxirane.

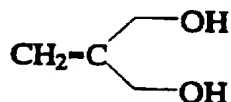


1.2.2.4

5

#### 1.2.2.5 2, 2-Bis(hydroxymethyl) oxirane

From 2-methylidene-1, 3-dihydroxypropanediol (commercially available).



1.2.2.5

10

#### 1.2.3 Preparation of Oxiranespiro-3-(1,5-Dioxacycloalkanes).

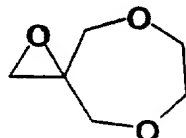
Various dry glycols in DMF were reacted with NaH and 3-chloromethyl-1-propane (1.2.2.0) was added to the resulting reaction mixture. Following completion of the reaction the solvents were removed and the product purified by low pressure distillation. The purified product in

15

## 29

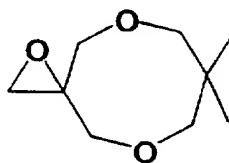
dichloroethane was reacted with m-chloroperbenzoic acid to form the corresponding epoxide. Following workup, the epoxide product was purified by distillation. The following compounds were prepared in this manner.

- 5      1.2.3.1      **Oxiranespiro-3-(1,5-dioxacycloheptane).**  
(From ethylene glycol)



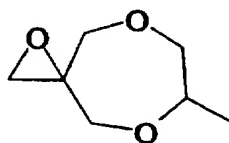
1.2.3.1

- 10      1.2.3.2      **Oxiranespiro-3-(1,5-dioxo-7,7-dimethylcyclooctane).**  
(From 2,2-dimethyl propylene glycol)



1.2.3.2

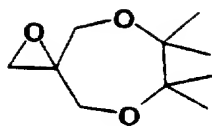
- 1.2.3.3      **Oxiranespiro-3-(1,5-dioxo-6-methylcycloheptane).**  
(From 1, 2- dihydroxy propane)



1.2.3.3

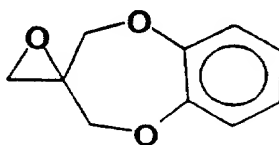
- 15      1.2.3.4      **Oxiranespiro-3-(1,5-dioxo-6,6,7,7-tetramethylcycloheptane).**  
[From 2,3-dihydroxy-2,3-dimethyl butane (pinacol)].

30



1.2.3.4

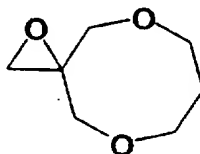
- 1.2.3.5 Oxiranespiro-3-(benzo[b]-1,5-dioxacycloheptane).**  
(From 1,2-dihydroxybenzene).



1.2.3.5

5

- 1.2.3.6 Oxiranespiro-3-(1,5-dioxacyclooctane).**  
(From 1,3-propanediol)

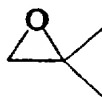


1.2.3.6

10

- 1.2.4 Preparation of Miscellaneous Epoxides**

- 1.2.4.1 2,2-dimethyl oxirane.**  
(From 2-methyl-1-propene and m-chloroperbenzoic acid.

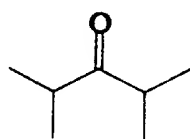


1.2.4.1

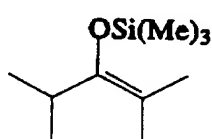
15

**1.2.4.2 2-(Isopropyl)-2-[(1-fluoro-1-methyl)ethyl] oxirane.**

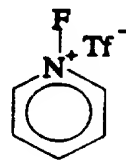
Reaction between 2,4-dimethyl-3-pentanone (1.2.4.3), trimethylsilyl chloride, and base gave 2,4-dimethyl-3-trimethylsilyloxy-2-pentene (1.2.4.4) which was reacted with 1-fluoropyridinium triflate (1.2.4.5) to form 2,4-dimethyl-2-fluoro-3-pentanone (1.2.4.6). This product was reacted with  $(\text{CH}_3)_3\text{S}(\text{O})^+\text{I}^-$  to form the title compound (1.2.4.2).



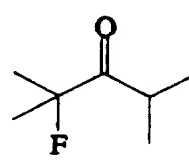
1.2.4.3



1.2.4.4



1.2.4.5



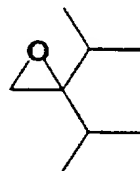
1.2.4.6



1.2.4.2

**1.2.4.7 2,2-Bis-isopropyl oxirane.**

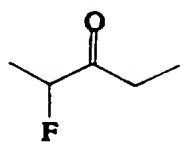
(From 2,4-dimethylpentanone using  $(\text{CH}_3)_3\text{S}(\text{O})^+\text{I}^-$  as described in 1.2.4.2)



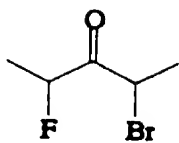
1.2.4.7

**1.2.4.8 2-(1-Fluoroethyl)-2-(1-trimethylsilyloxyethyl) oxirane.**

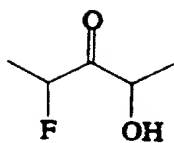
The title compound was obtained in several steps. DEK was O-silylated using usual procedure. The resulting product was reacted with 1-fluoropyridinium triflate (1.2.4.5) to yield 2-fluoro-3-pentanone (1.2.4.9). After bromination the 2-bromo-4-fluoro-3-pentanone (1.2.4.10) which was obtained was reacted with liquid ammonia to form 2-fluoro-4-hydroxy-3-pentanone (1.2.4.11). The free hydroxyl group was protected with trimethylsilylchloride to form 2-fluoro-4-trimethylsilyloxy-3-pentanone (1.2.4.12). This product was reacted with trimethylsulfoxonium iodide to form the title compound (1.2.4.8).



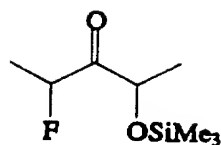
1.2.4.9



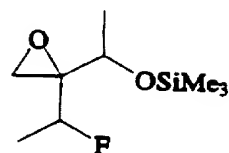
1.2.4.10



1.2.4.11



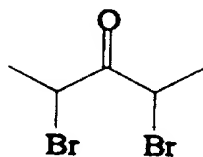
1.2.4.12



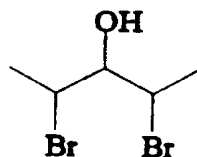
1.2.4.8

#### 1.2.4.13 2-(1-Bromoethyl)-3-methyl oxirane.

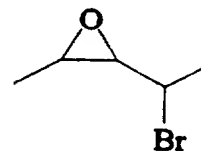
Bromination of diethyl ketone with bromine gave 2,4-dibromo-3-pentanone (1.2.4.14). This product was reduced with  $\text{BH}_3/\text{THF}$  to form 3-hydroxy-2,4-dibromopentane (1.2.4.15). After treatment with base the title compound (1.2.4.13) was obtained.



1.2.4.14



1.2.4.15



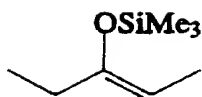
1.2.4.13

#### 1.2.4.16 2-(1-Fluoroethyl)-3-methyl oxirane.

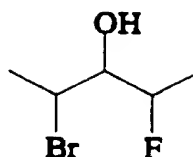
From reaction between diethylketone and trimethylchlorosilane to form 3-trimethylsilyloxy-2-pentene (1.2.4.17). This product was reacted with 1-fluoropyridinium triflate (1.2.4.5) to obtain 2-fluoro-3-pentanone (1.2.4.9). After bromination with pyridinium bromide followed by reduction using diborane 2-fluoro-4-bromopentane-3-ol (1.2.4.18) was obtained. Reaction of this product with sodium methylate yielded the title compound (1.2.4.16). This compound was made also by reacting 2-(1-bromoethyl)-3-methyl oxirane (1.2.4.13) with  $\text{HF}/\text{Py}$  (70%) followed by treatment of the resulting 2-bromo-4-fluoropentan-3-ol (1.2.4.18) with  $\text{K}_2\text{CO}_3/\text{MeOH}$ .

#### 1.2.4.19 2-(1-Fluoroethyl)-2-(1-methoxyethyl) oxirane.

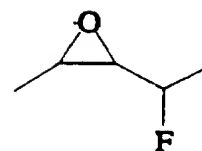
33



1.2.4.17



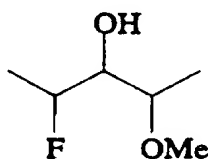
1.2.4.18



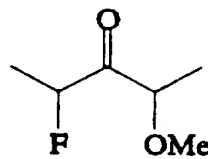
1.2.4.16

2-(1-Fluoroethyl)-3-methyl oxirane (1.2.4.16) was reacted with methanol/sulfuric acid to obtain 2-fluoro-4-methoxypentane-3-ol (1.2.4.20).

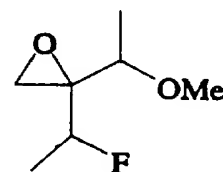
- 5 This product was reacted with chromic anhydride/pyridine to form 2-fluoro-4-methoxypentane-3-one (1.2.4.21) which was then reacted with sodium hydride and trimethylsulfoxonium iodide to obtain the title compound (1.2.4.19).



1.2.4.20



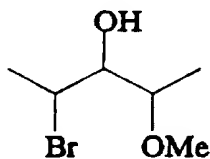
1.2.4.21



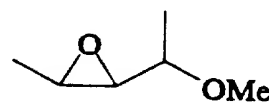
1.2.4.19

- 10 1.2.4.22 2-(1-Methoxyethyl)-3-methyl oxirane.

Reaction of 2-(1-Bromoethyl)-3-methyl oxirane (1.2.4.13) with methanol/sulfuric acid formed 2-bromo-3-hydroxy-4-methoxypentane (1.2.4.23). This product was reacted with potassium carbonate in methanol to obtain the title compound (1.2.4.22).



1.2.4.23

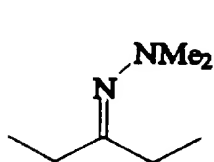


1.2.4.22

- 15 1.2.4.24 2-Ethyl-2-(1-methoxyethyl) oxirane.

Reaction between diethyl ketone and dimethyl hydrazine gave diethyl ketone-N,N-dimethylhydrazone (1.2.4.25). This product was reacted

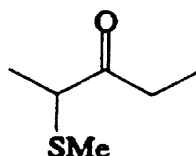
with dimethyl disulfide/LDA to obtain 2-methylthio-3-pentanone-N,N-dimethyl hydrazone (1.2.4.26). This product was reacted with mercuric chloride followed by cupric chloride to obtain 2-methoxy pentane-3-one (1.2.4.27). Reaction of the latter compound with sodium hydride/DMSO/trimethylsulfonium iodide yielded the title compound (1.2.4.24).



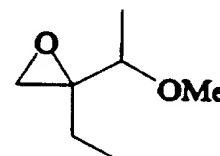
1.2.4.25



1.2.4.26



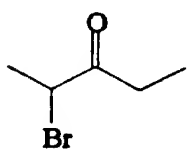
1.2.4.27



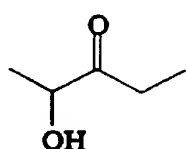
1.2.4.24

#### 1.2.4.28 2-Ethyl-2-(1-trimethylsilyloxyethyl) oxirane.

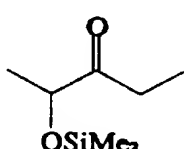
From reaction between 2-bromo-3-pentanone (1.2.4.29) and hydrazine obtained 2-hydroxy-3-pentanone (1.2.4.30). This product was reacted with trimethylchlorosilane/triethylamine to obtain 2-trimethylsilyloxy-3-pentanone (1.2.4.31). This product was reacted with methylenetriphenyl phosphite and butyllithium to obtain 2-ethyl-3-trimethylsilyloxy-1-butene (1.2.4.32). After oxidation with *meta*-chloroperbenzoic acid in methylene chloride the title compound (1.2.4.28) was obtained.



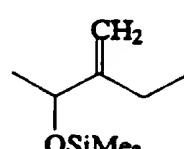
1.2.4.29



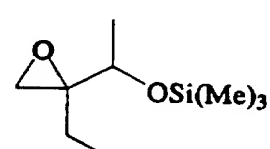
1.2.4.30



1.2.4.31



1.2.4.32



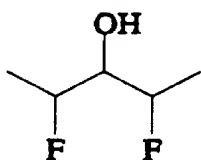
1.2.4.28

#### 1.2.4.33 2,2-Bis(1-fluoroethyl) oxirane.

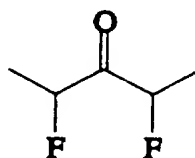
From reaction between 2-(1-Bromoethyl)-3-methyl oxirane (1.2.4.13) and HF/pyridine was obtained 2-bromo-4-fluoro-pentane-3-ol (1.2.4.18). This was reacted with potassium carbonate to obtain 2-(1-fluoroethyl)-3-methyl oxirane (1.2.4.16). This was reacted again with HF/pyridine to obtain 2,4-difluoro-pentane-3-ol (1.2.4.34). After oxidation with

## 35

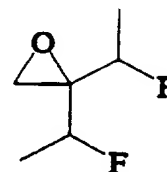
chromium trioxide obtained 2,4-difluoro-3-pentanone (1.2.4.35). The epoxide title compound was prepared from the ketone as described for 1.2.4.24.



1.2.4.34



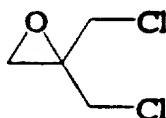
1.2.4.35



1.2.4.33

5      1.2.3.36      2,2-Bis-dichloromethyleneoxirane.

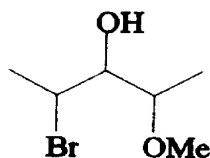
(From direct epoxidation of 3-chloro-2-chloromethyl-1-propene).



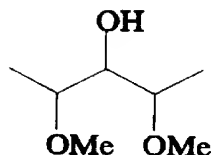
1.3.4.36

1.2.4.37      2,2-Bis(1-methoxyethyl) oxirane.

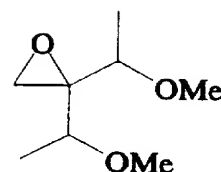
- 10      3-Pentanone was brominated to get 2,4-dibromo-3-pentanone (1.2.4.11) using conventional methods. The dibromoketone was reduced with  $\text{BH}_3 \cdot \text{THF}$  to the corresponding alcohol (1.2.4.15). This compound was reacted with  $\text{MeONa}$  in methanol to yield 2-(1-bromoethyl)-3-methyl oxirane (1.2.4.13) which after reaction with  $\text{MeOH}/\text{H}_2\text{SO}_4$  gave 2-bromo-3-hydroxy-4-methoxy pentane (1.2.4.38). This intermediate was reacted again with  $\text{MeONa}$  in methanol and the resulting 2-(1-methoxyethyl)-3-methyl oxirane (1.2.4.22) was reacted again with  $\text{MeOH}/\text{H}_2\text{SO}_4$  to yield 2,4-dimethoxy-3-hydroxy pentane (1.2.4.39). After oxidation with  $\text{CrO}_3/\text{Py}$  in methylenechloride the resulting ketone was reacted with trimethylsulfoxonium iodide to give the title compound (1.2.4.37).
- 15
- 20



1.2.4.38



1.2.4.39



1.2.4.37

### 1.2.5 Phosphite and Alkyl Phosphonate Esters.

Dialkylphosphites were prepared by reacting diethylphosphite with the corresponding alcohol.

#### 1.2.5.1 Di-n-butylphosphite, $\text{HP(O)[OCH}_2(\text{CH}_2)_2\text{CH}_3]_2$

(From n-butyl alcohol)

#### 1.2.5.2 Dioctylphosphite, $\text{HP(O)[OCH}_2(\text{CH}_2)_6\text{CH}_3]_2$ .

(From octyl alcohol)

#### 1.2.5.3 Diisobutylphosphite, $\text{HP(O)(O}^i\text{Bu)}_2$ .

(From iso butyl alcohol)

#### 1.2.5.4 Dibenzyl phosphite, $\text{HP(O)(OCH}_2\text{Ph)}_2$ .

(From benzyl alcohol).

#### 1.2.5.5 Diethyl(2-bromoethyl) phosphonate, $\text{BrCH}_2\text{CH}_2\text{P(O)(OEt)}_2$ .

(From reaction between triethylphosphite and 1,2-dibromomethane)

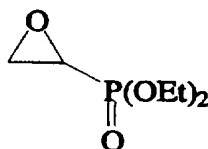
#### 1.2.5.6 Diethyl(2-chloro-1-hydroxyethyl) phosphonate,



(From reaction of diethylphosphite and chloroacetaldehyde).

#### 1.2.5.7 2-(Diethylphosphonate) oxirane.

(From 1.2.5.6, sodium ethoxide).



1.2.5.7

### 1.2.6 Halides and Tosylates

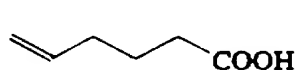
#### 1.2.6.1 1-Bromo-2-hydroxy-3,3-dimethylbutane, $\text{BrCH}_2\text{CH(OH)C(CH}_3)_2$

(From reduction of bromomethyl-t-butyl ketone by  $\text{BH}_3/\text{THF}$ ).

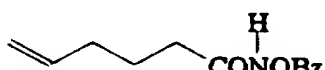
**1.2.6.2 1-Bromo-2-t-butyldimethylsilyloxyethane,  $\text{BrCH}_2\text{CH}_2\text{Si}(\text{t-Bu})(\text{CH}_3)_2$**   
(From bromoethanol and dimethyl-t-butyldimethylsilylchloride)

**1.2.6.3 5-(p-Toluenesulfonyloxymethylene)-1-benzyloxy-2-pyrrolidone.**

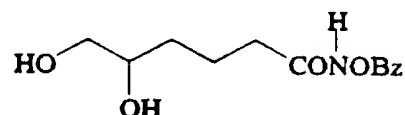
This compound was prepared in several steps. 4-pentenoic acid (1.2.6.4) was reacted with ethylchloroformate in the usual way to obtain the active mixed anhydride. To a solution of the mixed anhydride in chloroform was added triethylamine and O-benzylhydroxylamine hydrochloride to obtain O-benzyl-4-pentenohydroxamic acid (1.2.6.5). The double bond was oxidized using osmium tetroxide/N-methylmorpholine oxide to give the diol (1.2.6.6). The terminal hydroxyl group was then protected with t-butyldimethylsilylchloride in the usual way to yield (1.2.6.7). The secondary hydroxyl group was tosylated using pyridine/p-toluenesulfonyl chloride. Cyclization of (1.2.6.8) to the corresponding pyrrolidone (1.2.6.9) was effected by using sodium carbonate in methanol. The protecting silyl group was removed by treatment with tetraethylammonium fluoride. The title compound (1.2.6.3) was prepared by reacting the latter compound (1.2.6.10) with pyridine/p-toluenesulfonyl chloride in the usual way.



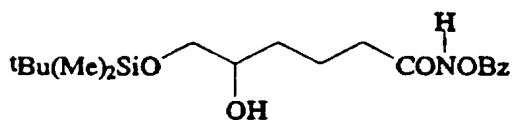
1.2.6.4



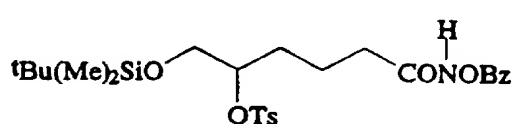
1.2.6.5



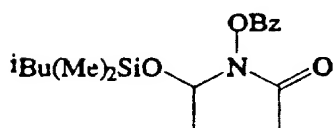
1.2.6.6



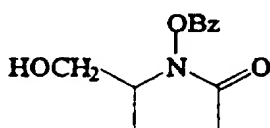
1.2.6.7



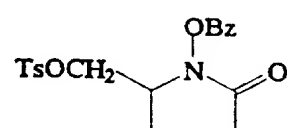
1.2.6.8



1.2.6.9



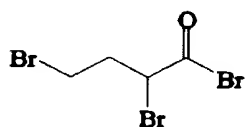
1.2.6.10



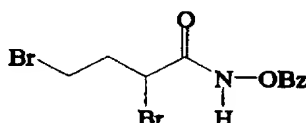
1.2.6.3

**1.2.6.11 5-Bromo-1-benzyloxy-2-pyrrolidone.**

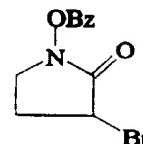
This compound was prepared in several steps. Butyrolactone was reacted with  $\text{PBr}_3/\text{Br}_2$  to obtain the dibromobutyrylbromide (1.2.6.12). This compound with O-benzylhydroxylamine yielded the protected dibromohydroxamic acid (1.2.6.13). Cyclization was effected by base to give the cyclic protected hydroxamic acid (1.2.6.11).



1.2.6.12



1.2.6.13



1.2.6.11

**1.2.7 Preparation of N-Alkyl-O-Benzylchloroacetohydroxamic Acids.**

This class of compounds was prepared from chloroacetyl chloride and the suitable N-Alkylhydroxylamine followed by O-benylation with benzyl bromide. In certain instances the O-benzyl alkylhydroxylamine was used as the starting material. O-Methyl chloroacetoxhydroxamic acid was prepared employing O-methylhydroxylamine as starting material.

**1.2.7.1 O-Benzyl-N-Methyl Chloroacetohydroxamic acid,**  
 $\text{ClCH}_2\text{CON}(\text{Me})(\text{OBz}).$

**1.2.7.2 O-Benzyl-N-isopropyl-Chloroacetohydroxamic acid,**  
 $\text{ClCH}_2\text{CON}(\text{iPr})(\text{OBz}).$

**1.2.7.3 O-Benzyl-N-tert-butyl-Chloroacetohydroxamic acid,**  
 $\text{ClCH}_2\text{CON}(\text{tBu})(\text{OBz}).$

**1.2.7.4 O-Benzyl Chloroacetohydroxamic acid,**  $\text{ClCH}_2\text{CONH}(\text{OBz})$

**1.2.7.5 O-Methyl chloroacetohydroxamic acid,**  $\text{ClCH}_2\text{CONH}(\text{OMe})$

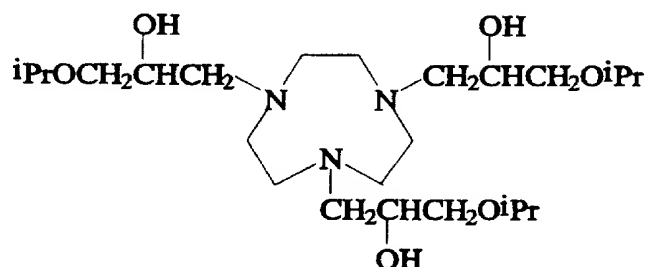
**1.3 SYNTHESIS OF CHELATORS (LIGANDS)****1.3.1 Synthesis of Polyaza Ligands with Pendant Arms Containing  $\beta$ -Hydroxy Groups and Their Derivatives.**

This family of compounds was prepared by reacting polyaza free bases with epoxides or halohydrines in water or alcohol solvents.

39

**1.3.1.1      N,N',N''-Tris (2-hydroxy-3-isopropoxypropyl)-1,4,7-Triazacyclononane.**

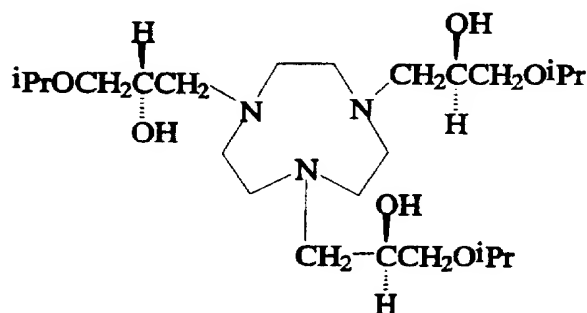
From 1,4,7-triazacyclononane (1.1.3) and d,l-glycidyl isopropyl ether (1.2.1.2).



1.3.1.1

**1.3.1.2      (R,R,R) N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and (2R) glycidyl isopropyl ether (1.2.1.3).

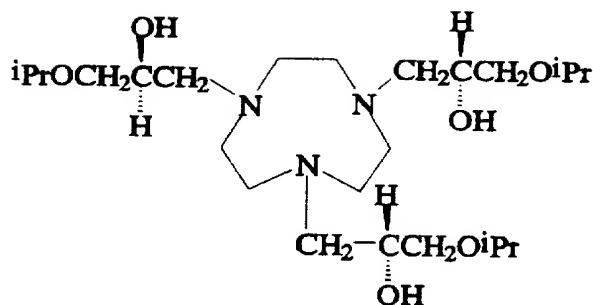


1.3.1.2

**1.3.1.3      (S,S,S) N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane and (2S) glycidyl isopropyl ether (1.2.1.4).

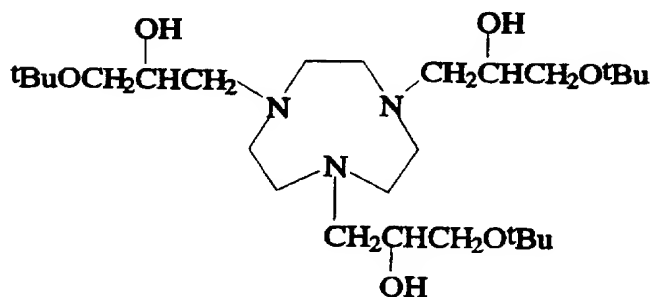
40



1.3.1.3

**1.3.1.4 N,N',N''-Tris(2-hydroxy-3-t-butoxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.13) and (d,l) glycidyl-t-Butyl ether (1.2.1.5).

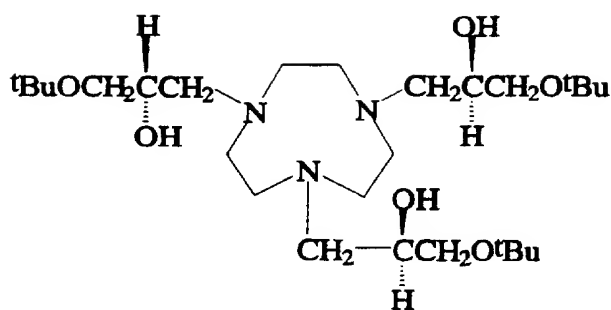


1.3.1.4

**1.3.1.5 (R,R,R) N,N',N''-Tris(2-hydroxy-3-t-butoxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and (R) glycidyl t-Butyl ether (1.2.1.6).

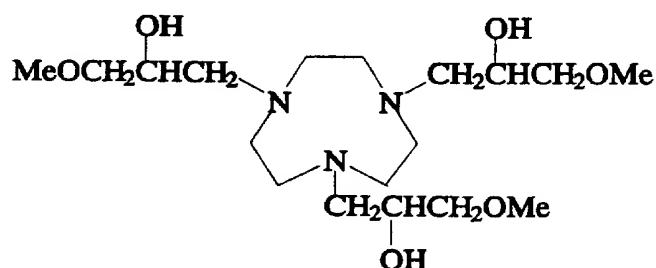
41



1.3.1.5

**1.3.1.6 N,N',N''-Tris(2-hydroxy-3 methoxypropyl)-1,4,7-triazacyclononane**

From 1,4,7-Triazacyclononane (1.1.3) and (d,l) glycidyl methyl ether (commercially available).

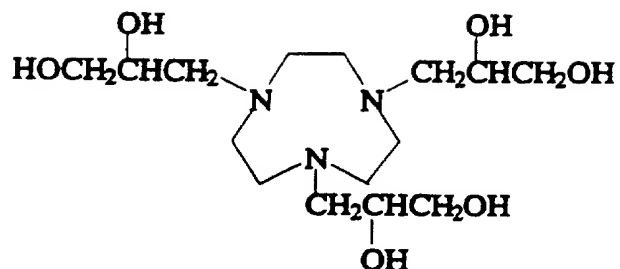


1.3.1.6

**1.3.1.7 N,N',N''-Tris(2,3-dihydroxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 1-bromo-2,3-dihydroxypropane (commercially available) and excess of potassium carbonate or 1-chloro-2,3-dihydroxypropane (commercially available) and base.

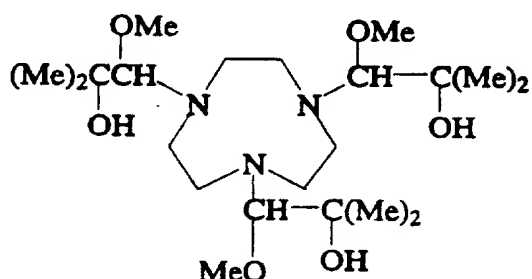
42



1.3.1.7

**1.3.1.8 N,N',N''-Tris(1-methoxy-2-hydroxy-2-methylpropyl)-1,4,7-triazacyclononane.**

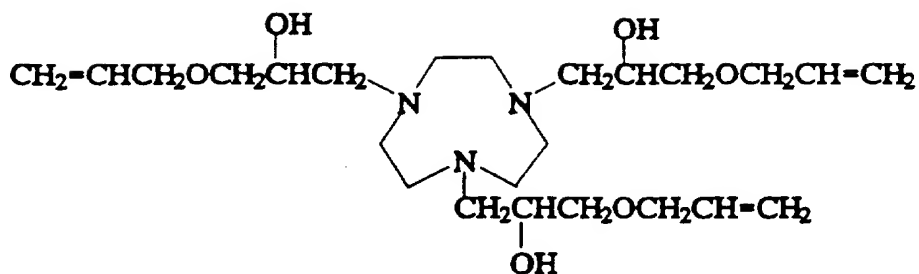
From 1,4,7-Triazacyclononane (1.1.3) and (d, l) 3,3-Dimethyl-2-methoxy oxirane (1-methoxy-2-methylpropylene, commercially available).



1.3.1.8

**1.3.1.9 N,N',N''-Tris(2-hydroxy-3-allyloxypropyl)-1,4,7-triazacyclononane.**  
From 1,4,7-Triazacyclononane (1.1.3) and (d,l) glycidyl allyl ether (1.2.1.7).

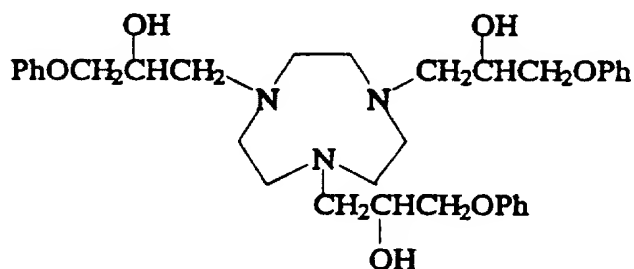
43



1.3.1.9

**1.3.1.10 N,N',N''-Tris(2-hydroxy-3-phenoxypropyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and (d,l) glycidyl phenyl ether (1.2.1.8).

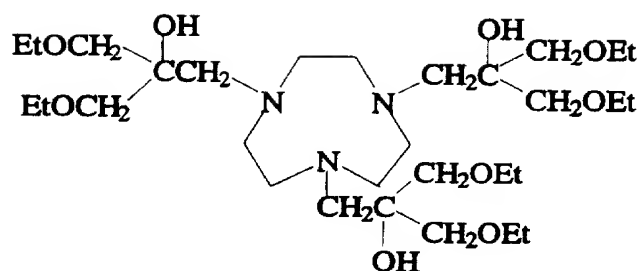


1.3.1.10

**1.3.1.11 N,N',N''-Tris(2-hydroxy-2,2-diethoxymethylene)ethyl-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis-ethoxymethyl oxirane(1.2.2.1).

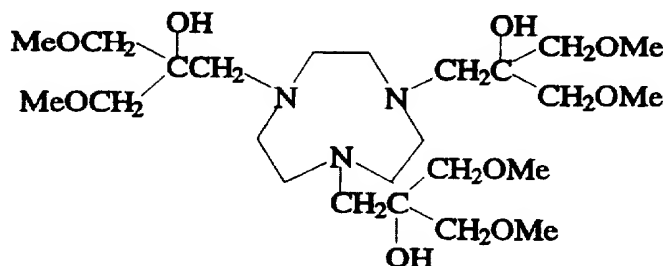
44



1.3.1.11

**1.3.1.12 N,N',N''-Tris(2-hydroxy-2,2-dimethoxymethyl)ethyl-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis-methoxyoxymethyl oxirane (1.2.2.2).

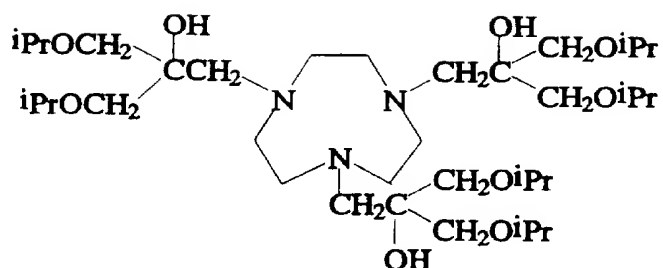


1.3.1.12

**1.3.1.13 N,N',N''-Tri(2-hydroxy-(2,2-diisopropoxy)methyl)ethyl-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis-isopropoxyxymethyl oxirane (1.2.2.3).

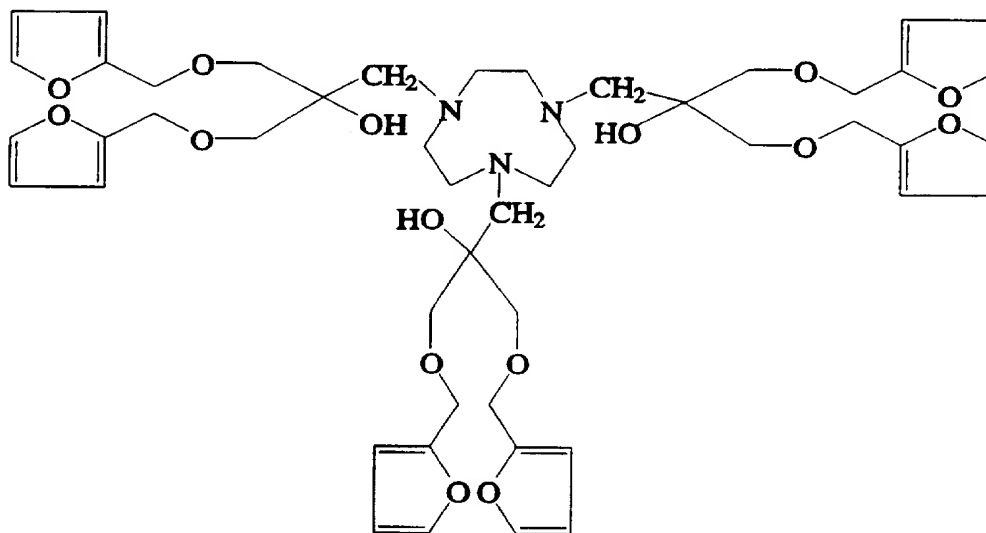
45



1.3.1.13

**1.3.1.14 N,N',N''-Tris[2-hydroxy-bis(2-furfuryloxymethyl)ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-Bis(furfurylmethyl)oxirane (1.2.2.4).

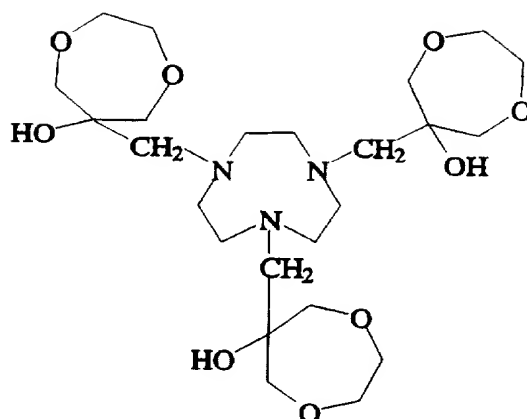


1.3.1.14

**1.3.1.15 N,N',N''-Tris(3-hydroxy-1,5-dioxacycloheptyl-3-methyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxacycloheptane) (1.2.3.1).

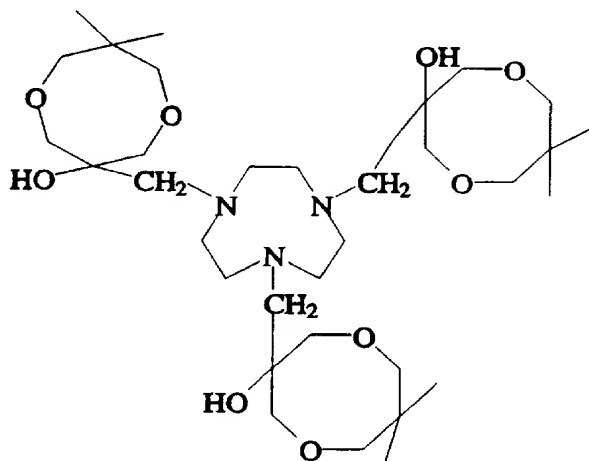
46



1.3.1.15

**1.3.1.16     N,N',N''-Tris[(3-Hydroxy-7,7-dimethyl-1,5-dioxacyclooct-3-yl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxa-7,7-dimethylcyclooctane) (1.2.3.2).

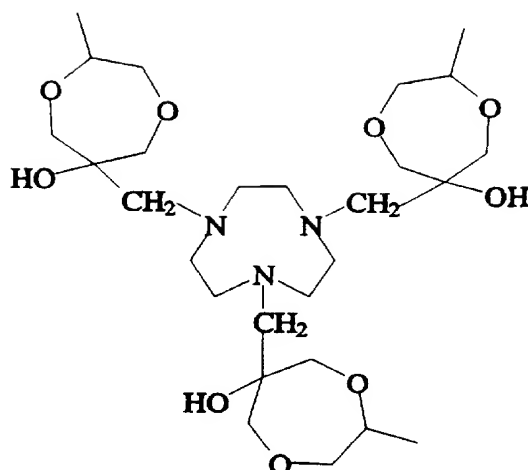


1.3.1.16

**1.3.1.17     N,N',N''-Tris[(3-hydroxy-7-methyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and Oxiranespiro-3-(1,5-dioxa-6-methylcycloheptane) (1.2.3.3).

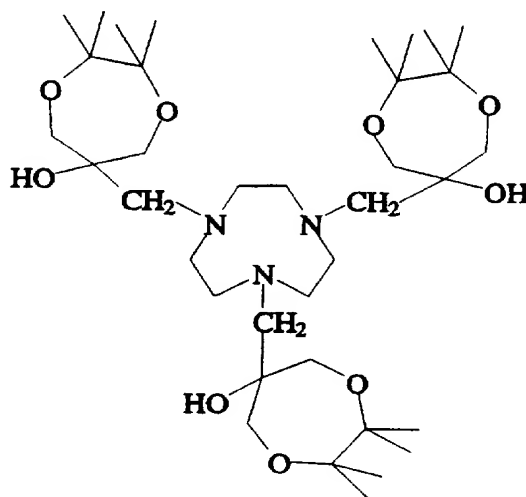
47



1.3.1.17

**1.3.1.18 N,N',N''-Tris[(3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-Triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxa-6,6,7,7-tetramethylcycloheptane) (1.2.3.4).

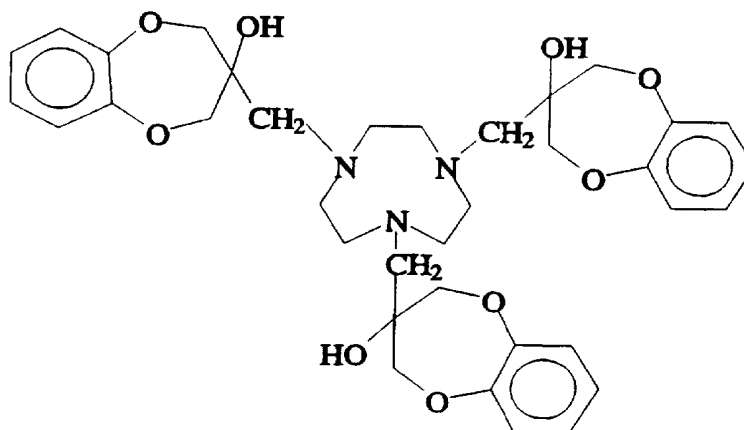


1.3.1.18

**1.3.1.19 N,N',N''-Tris[(3-hydroxy-benzo[b]-1,5-dioxacycloheptyl)methyl]1,4,7-triazacyclononane.**

48

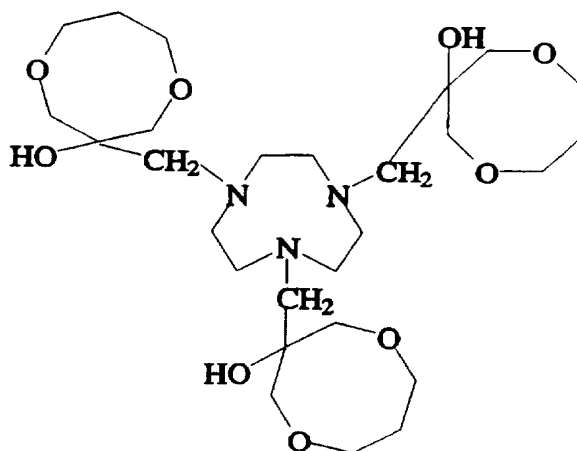
From 1,4,7-triazacyclononane (1.1.3) and oxiranespiro-3-(benzo[b]-1,5-dioxacycloheptane) (1.2.3.5).



1.3.1.19

**1.3.1.20**    **N,N',N''-Tris[(3-hydroxy-1,5-dioxacyclooctane-3-yl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and oxiranespiro-3-(1,5-dioxacyclooctane) (1.2.3.6).

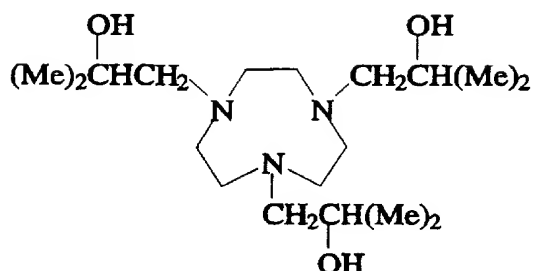


1.3.1.20

**1.3.1.21**    **N,N',N''-Tris(2-hydroxy-2-methylpropyl)-1,4,7-Triazacyclononane.**

49

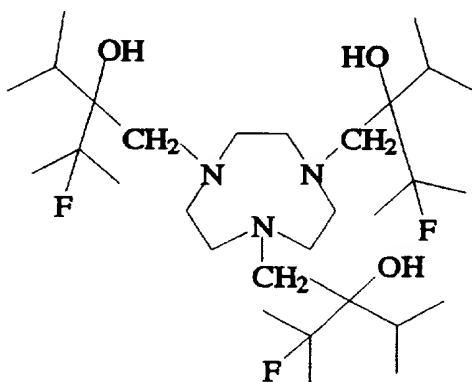
From 1,4,7-Triazacyclononane (1.1.3) and 2,2-Dimethyl oxirane (1.2.4.1 )



1.3.1.21

**1.3.1.22 N,N',N''-Tris[(4-fluoro-2-hydroxy-3-i-propyl-4-methyl)pentyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-isopropyl-2-(1-fluoro-1-methylethyl) oxirane (1.2.4.2).

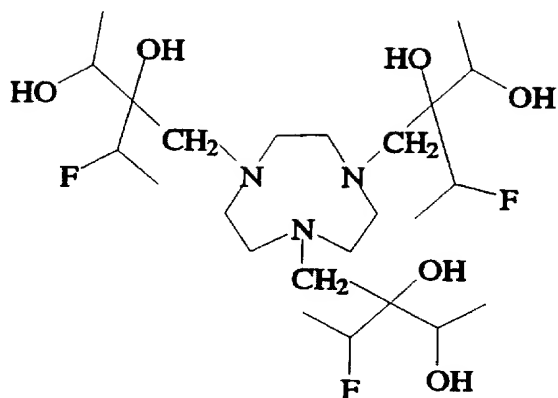


1.3.1.22

**1.3.1.23 N,N',N''-Tris-[2-hydroxy-3-(1-fluoroethyl)-4-hydroxypentyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-(1-trimethylsilyloxyethyl)-2-(1-fluoroethyl) oxirane (1.2.4.8).

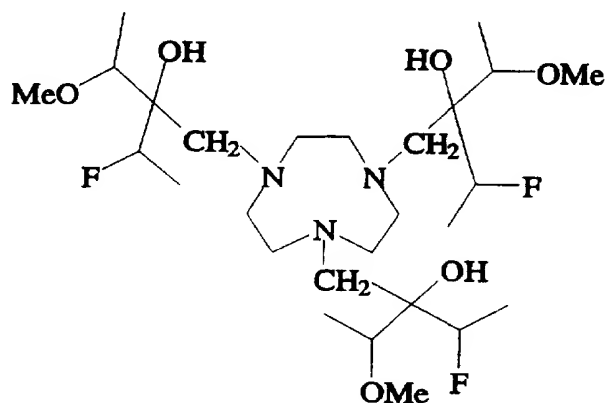
50



1.3.1.23

**1.3.1.24     N,N',N''-Tris[2-hydroxy-2-(1-fluoroethyl)-2-(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-(1-Fluoroethyl)-2-(1-methoxyethyl) oxirane (1.2.4.19).

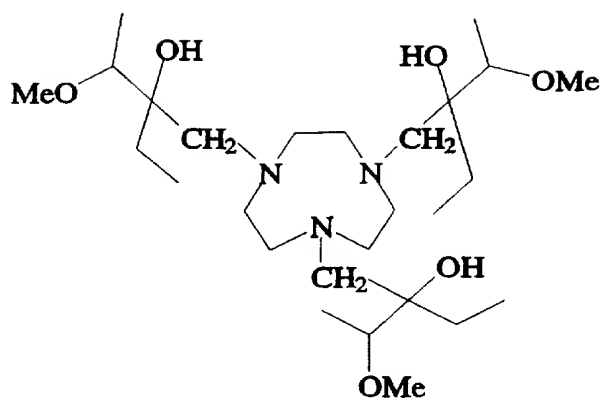


1.3.1.24

**1.3.1.25     N,N',N''-Tris(2-hydroxy-2-ethyl-3-methoxy butyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-ethyl-2-(1-methoxyethyl) oxirane (1.2.4.24).

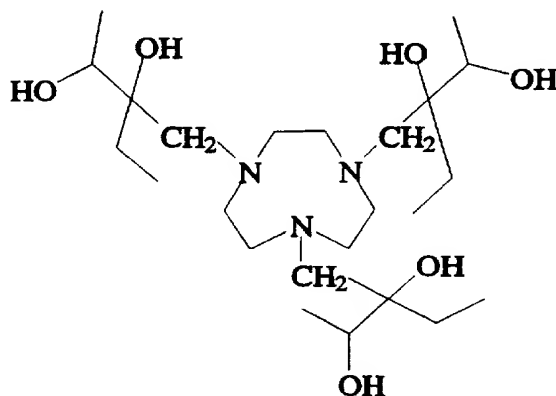
51



1.3.1.25

**1.3.1.26 N,N',N''-Tris(2,3-dihydroxy-2-ethyl)butyl]-1,4,7-Triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2-ethyl-2-(1-trimethylsilyloxyethyl) oxirane (1.2.4.28).

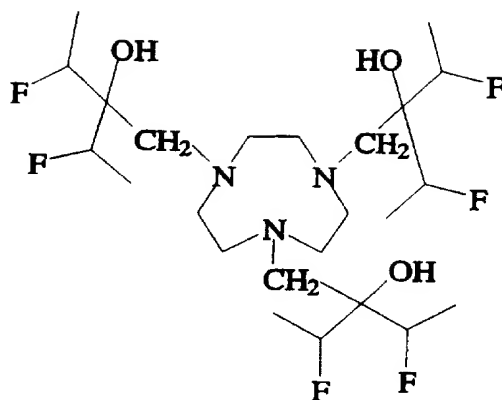


1.3.1.26

**1.3.1.27 N,N',N''-Tris[2-hydroxy-2,2-bis(1-fluoro ethyl) ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-bis(1-fluoroethyl) oxirane (1.2.4.33).

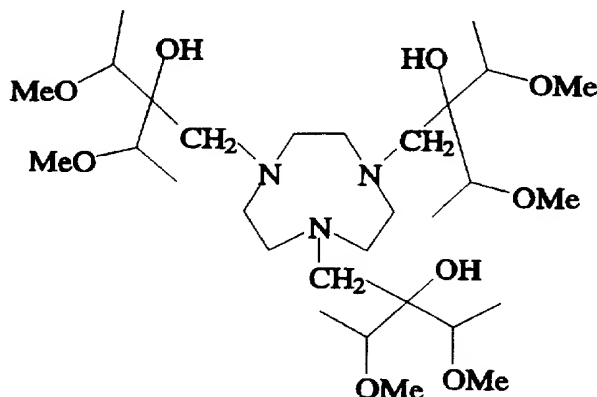
52



1.3.1.27

**1.3.1.28     N,N',N''-Tris[2-hydroxy-2,2-bis(1-methoxyethyl) ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3) and 2,2-(1-methoxyethyl) oxirane (1.2.4.37).

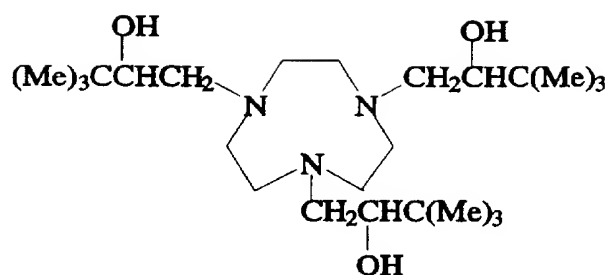


1.3.1.28

**1.3.1.29     N,N',N''-Tris[(3,3-dimethyl-2-hydroxy)butyl]-1,4,7-triazacyclononane.**

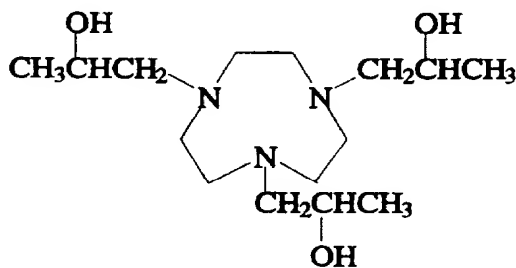
From 1,4,7-Triazacyclononane (1.1.3), 1-Bromo-2-hydroxy-3,3-dimethylbutane (1.2.6.1) and sodium carbonate.

53



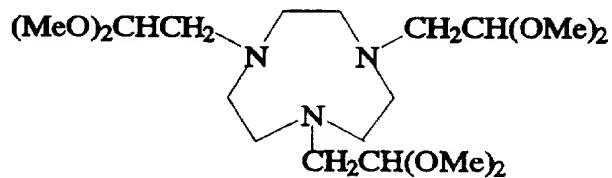
1.3.1.29

- 1.3.1.30 N,N',N''-Tris(2-hydroxypropyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and propylene oxide.



1.3.1.30

- 1.3.1.31 N,N',N''-Tris(2,2-dimethoxyethyl)-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3), 1-chloro-2,2-dimethoxyethane (commercially available) and sodium carbonate.

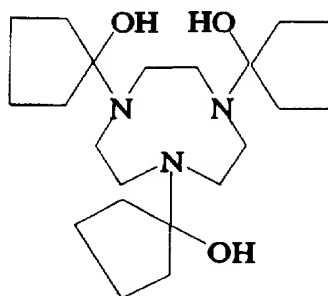


1.3.1.31

- 1.3.1.32 N,N',N''-Tris(2-hydroxycyclopentan-1-yl)-1,4,7-triazacyclononane.**

54

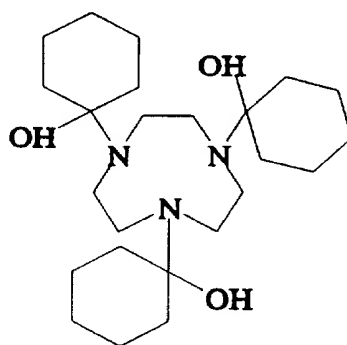
From 1,4,7-triazacyclononane (1.1.3), 1,2-epoxycyclopentane (commercially available) and sodium carbonate.



1.3.1.32

**1.3.1.33     N,N',N''-Tris(2-hydroxycyclohexane-1-yl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), 1,2-epoxycyclohexane (commercially available) and sodium carbonate.

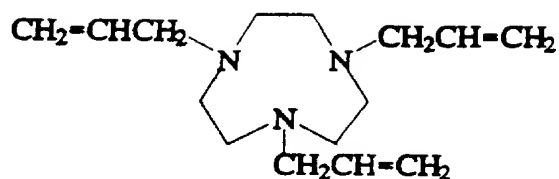


1.3.1.33

**1.3.1.34     N,N',N''- Trivinyl-1,4,7-Triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), sodium hydride and vinyl bromide.

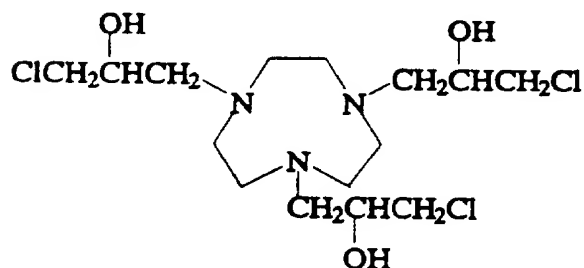
55



1.3.1.34

**1.3.1.35 N,N',N''-Tris[(3-chloro-2-hydroxy)propyl]-1,4,7-Triazacyclononane.**

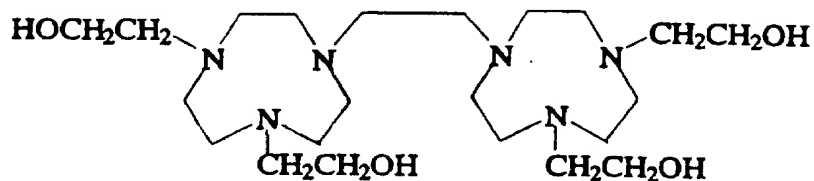
From N,N',N''-triallyl-1,4,7-triazacyclononane(1.3.1.34) and aqueous chlorine.



1.3.1.35

**1.3.1.36 1,2-Bis-(N,N'-di-2-hydroxyethyl-1,4,7-triazacyclononane-1-yl) ethane.**

From 1,2-bis-(1,4,7-triazacyclononane-1-yl) ethane polyhydrobromide and ethylene oxide.

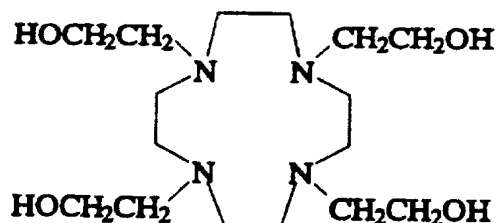


1.3.1.36

56

**1.3.1.37    N,N',N'',N'''-Tetrakis-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane.**

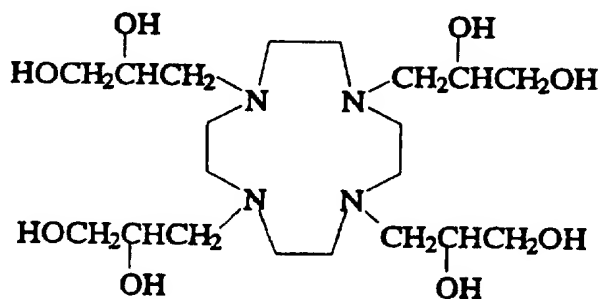
From 1,4,7,10-Tetraazacyclododecane (1.1.4) and bromoethanol.



1.3.1.37

**1.3.1.38    N,N',N'',N'''-Tetrakis(2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclotetradecane.**

From 1,4,7,10-tetraazacyclotetradecane (1.1.4), 1-chloro-2,3-propanediol (commercially available) and base.

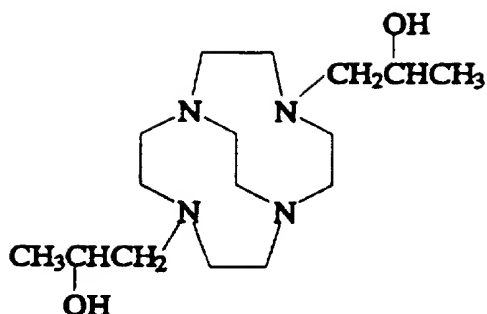


1.3.1.38

**1.3.1.39    4,10-Bis(2-Hydroxypropyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.4) and propylene oxide.

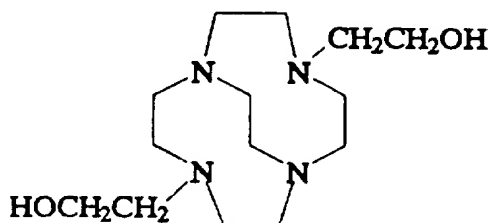
57



1.3.1.39

**1.3.1.40** 4,10-Bis-(2-hydroxyethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.

From 4,10-Bis(dimethoxycarbonylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.6.8) and lithium aluminum hydride.

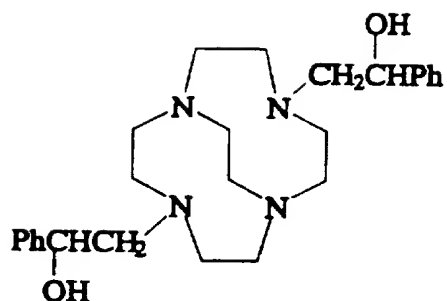


1.3.1.40

**1.3.1.41** 4,10-Bis[(2-Hydroxy-2-phenyl)ethyl]-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.

From 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (1.1.4) and styrene oxide.

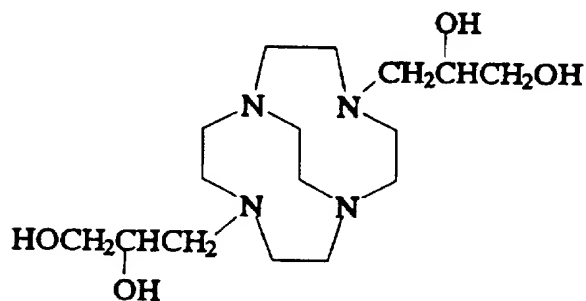
58



1.3.1.41

**1.3.1.42 4,10-Bis-(2,3-dihydroxypropyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

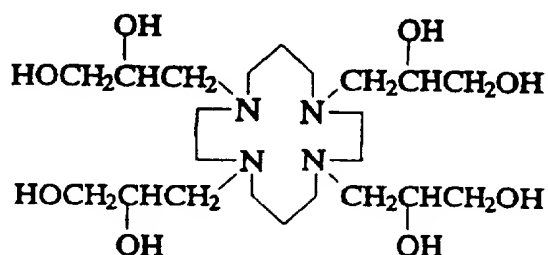
From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.4) and glycidol.



1.3.1.42

**1.3.1.43 N,N',N'',N'''-Tetrakis-(2,3-dihydroxypropyl)-1,4,8,11-tetraazacyclohexadecane.**

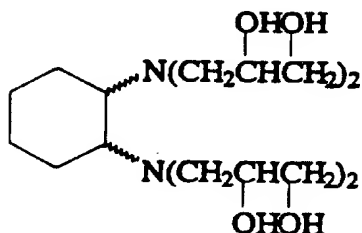
From cyclam (1.1.5) and glycidol.



1.3.1.43

**1.3.1.44** *cis, trans N,N,N',N'*-Tetrakis(2,3-dihydroxypropyl)-1,2-diamino-cyclohexane.

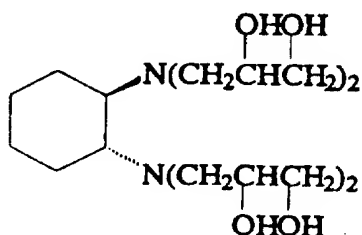
From *cis,trans* 1,2-diaminocyclohexane (commercially available) and glycidol.



1.3.1.44

**1.3.1.45** *trans N,N,N',N'*-Tetrakis(2,3-dihydroxypropyl)-1,2-diamino-cyclohexane.

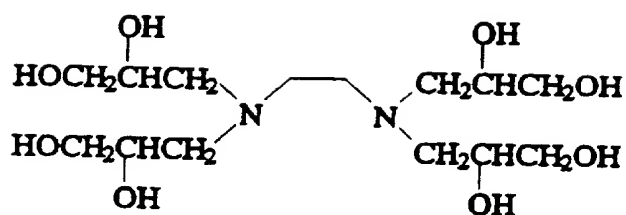
From *trans*-1,2-diaminocyclohexane (commercially available) and glycidol.



1.3.1.45

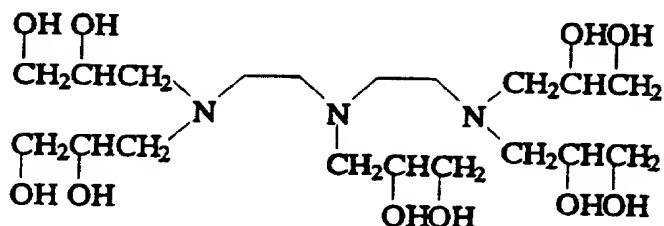
**1.3.1.46.** *N,N,N',N'*-Tetrakis(2,3-dihydroxypropyl)-ethylenediamine.

From ethylenediamine (1.1.0) and glycidol.



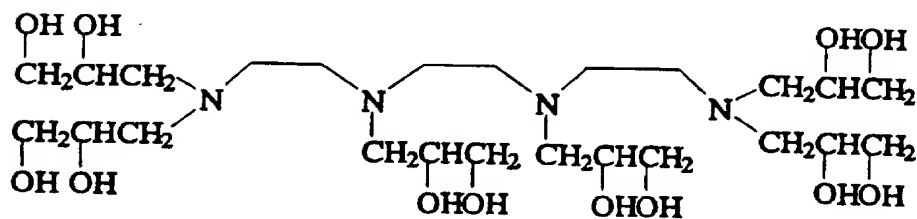
1.3.1.46

- 1.3.1.47 N,N,N',N'',N'''-Pentakis(2,3-dihydroxypropyl)-diethylenetriamine.**  
From diethylenetriamine (1.1.1), 1-chloro-2,3-propanediol and base.



1.3.1.47

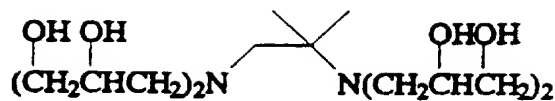
- 1.3.1.48 N,N,N',N'',N''',N'''-Hexakis(2,3-dihydroxypropyl) triethylenetetramine.**  
From triethylenetetramine (1.1.2) and glycidol.



1.3.1.48

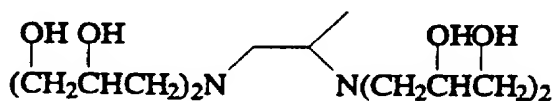
- 1.3.1.49 N,N,N',N'-Tetrakis(2,3-dihydroxypropyl)-1,2-diamino-2-methylpropane.**  
From 1,2-diaminomethylpropane and glycidol.

61



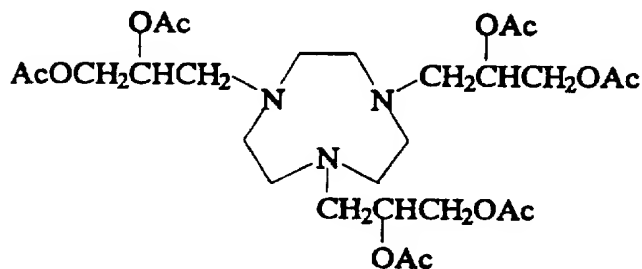
1.3.1.49

- 1.3.1.50** **N,N,N',N'-Tetrakis(2,3-dihydroxypropyl)-1,2-diaminopropane.**  
From 1,2-diaminopropane and glycidol.



1.3.1.50

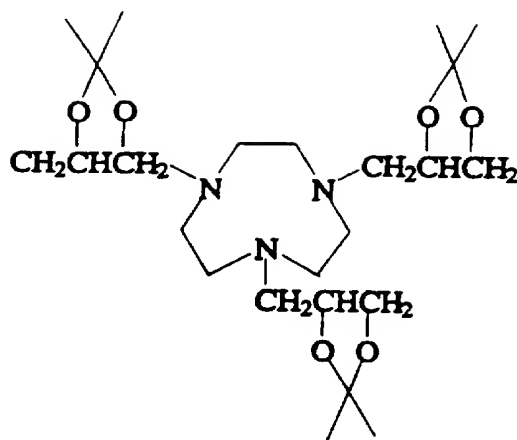
- 1.3.1.51** **N,N',N''-Tris(2,3-diacetoxypentyl)-1,4,7-triazacyclononane.**  
From 1.3.1.7 and Py/Ac<sub>2</sub>O.



1.3.1.51

- 1.3.1.52** **N,N',N''-tris(Dimethyl-2,3-isopropylidene propyl)-1,4,7-triazacyclononane.**  
From 1.3.1.7 and 2,2-dimethoxypropane/p-toluenesulfonic acid.

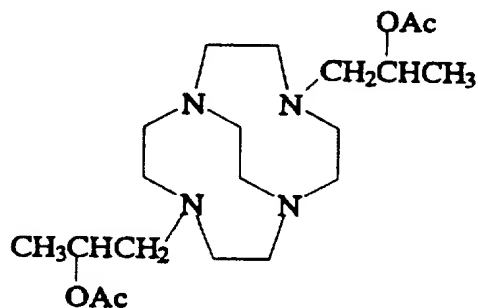
62



1.3.1.52

**1.3.1.53** 4,10-(2-Diacetoxypropyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.

From 1.3.1.39 and Py/Ac<sub>2</sub>O.

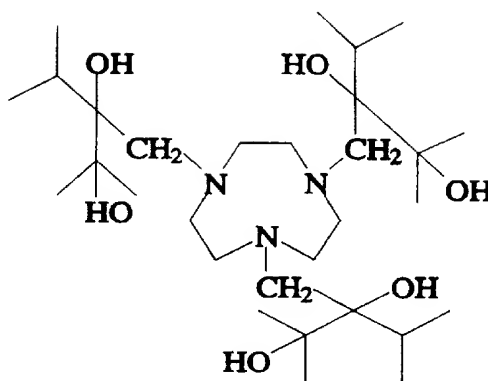


1.3.1.53

**1.3.1.54** N,N',N''-Tris[(2,4-dihydroxy-3-isopropyl-4-methyl)pentyl]-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3) and 2,2-bis(hydroxymethyl) oxirane.

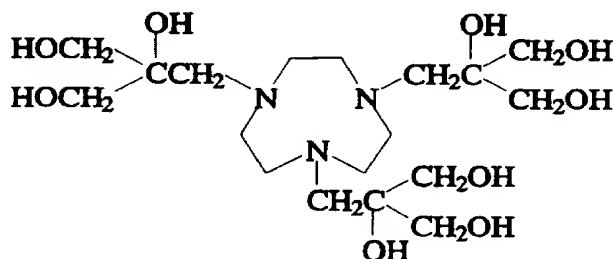
63



1.3.1.54

**1.3.1.55     N,N',N''-Tris-[2-hydroxy-(2,2-dihydroxymethyl)ethyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) and 2,2-bis(hydroxymethyl)oxirane (1.2.2.5).



1.3.1.55

**1.3.2            Synthesis of Polyaza Ligands With Alkylphosphonate Mono- and Di-Esters Pendant Arms.**

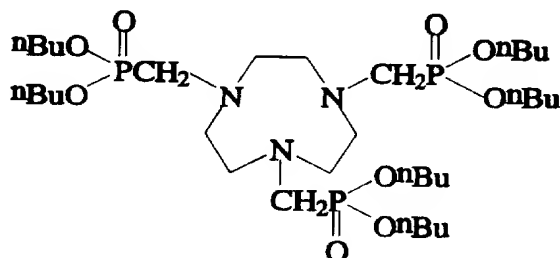
**1.3.2.1          Preparation**

Chelators which have three identical methylene phosphonate diester arms were prepared by reacting the trihydrobromide polyaza bases with formaldehyde and dialkylphosphite. The hexa-ester was hydrolyzed to the tri-

ester by heating with NaOH dissolved in the appropriate alcohol (the same R group as in the dialkylphosphite). In some cases products were obtained by reacting the amine base with haloalkylphosphonates or epoxyposphonates.

**1.3.2.1 N,N',N''-Tris(dibutylphosphorylmethyl)-1,4,7-triazacyclononane.**

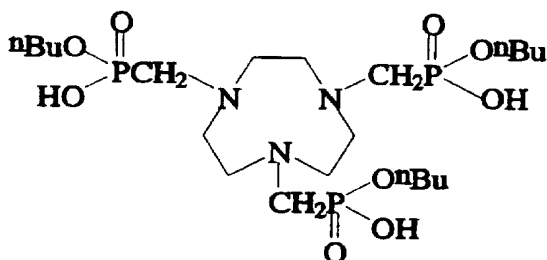
From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, formaldehyde solution and di-n-butyl phosphite (1.2.5.1).



1.3.2.1

**1.3.2.2 N,N',N''-Tris(dihydroxyphosphorylmethyl mono butyl ester)-1,4,7-triazacyclononane.**

From N,N',N''-tris(dibutylphosphorylmethyl)-1,4,7-triazacyclononane (1.3.2.1) and KOH/butanol.

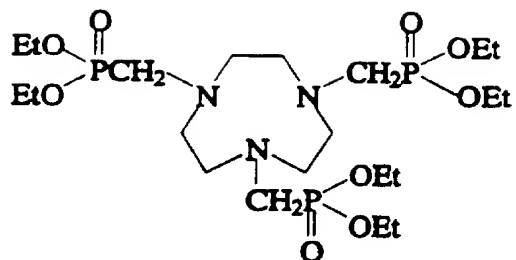


1.3.2.2

**1.3.2.3 N,N',N''-Tris(diethylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, formaldehyde solution and diethyl phosphite (commercially available).

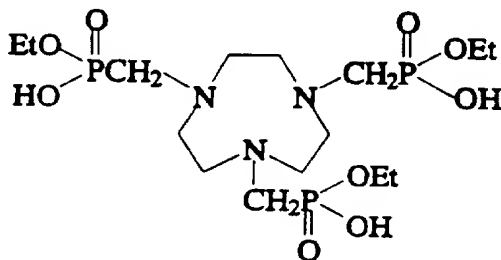
65



1.3.2.3

**1.3.2.4 N,N',N''-Tris(dihydroxyphosphorylmethyl monoethyl ester)-1,4,7-triazacyclononane.**

From N,N',N''-tris(diethylphosphorylmethyl)-1,4,7-triazacyclononane (1.3.2.3) and NaOH/EtOH.

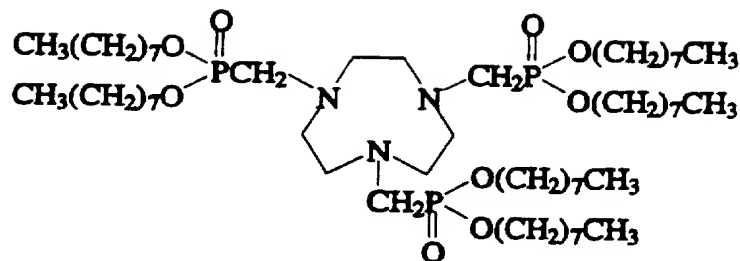


1.3.2.4

**1.3.2.5 N,N',N''-Tris(dioctylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), formaldehyde and dioctylphosphite (1.2.5.2).

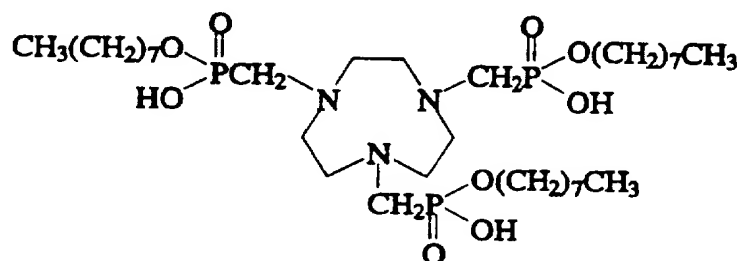
66



1.3.2.5

**1.3.2.6      N,N',N''-Tris(dihydroxyphosphorylmethyl mono-octyl ester)-1,4,7-triazacyclononane.**

From 1.3.2.5 and NaOH in octyl alcohol.

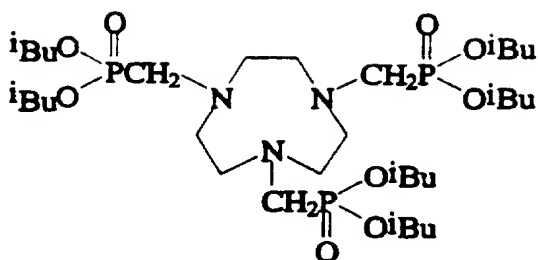


1.3.2.6

**1.3.2.7      N,N',N''-Tris(diisobutylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3), formaldehyde and diisobutylphosphite (1.2.5.3).

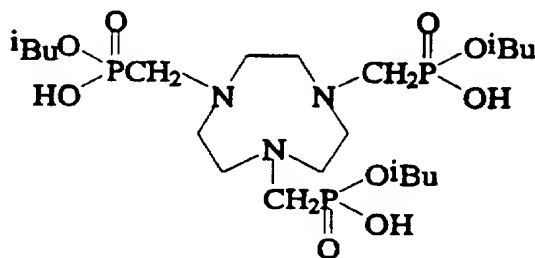
67



1.3.2.7

**1.3.2.8      N,N',N''-Tris(dihydroxyphosphorylmethyl monoisobutyl ester)-1,4,7-triazacyclononane.**

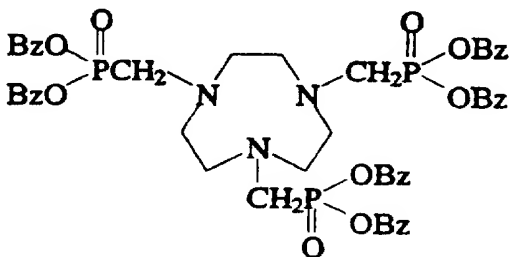
From 1.3.2.7 and NaOH in isobutyl alcohol.



1.3.2.8

**1.3.2.9      N,N',N''-Tris(dibenzylphosphorylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane (1.1.3), formaldehyde and dibenzylphosphite (1.2.5.4).

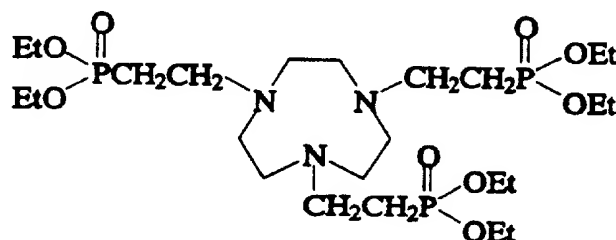


1.3.2.9

68

**1.3.2.10 N,N',N''-Tris(diethylphosphorylethyl)-1,4,7-triazacyclononane.**

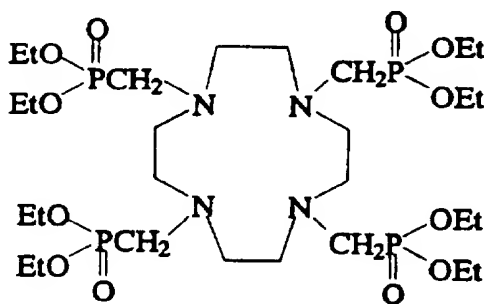
From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, potassium carbonate and diethyl(2-bromoethyl)phosphonate (1.2.5.5).



1.3.2.10

**1.3.2.11 N,N',N'',N'''-Tetrakis(diethylphosphorylmethyl)-1,4,7,10-Tetraazacyclodecane.**

From 1,4,7,10-Tetraazacyclodecane (1.1.4) trihydrobromide, formaldehyde and diethylphosphite (commercially available).

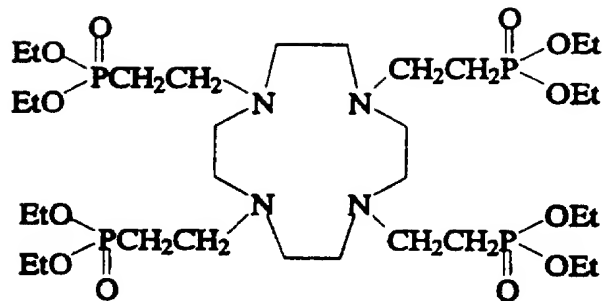


1.3.2.11

**1.3.2.12 N,N',N'',N'''-Tetrakis(diethylphosphorylethyl)-1,4,7,10-tetraazacyclododecane.**

From 1,4,7,10-tetraazacyclododecane (1.1.4) trihydrobromide, potassium carbonate and diethyl(2-bromoethyl)phosphonate (1.2.5.5).

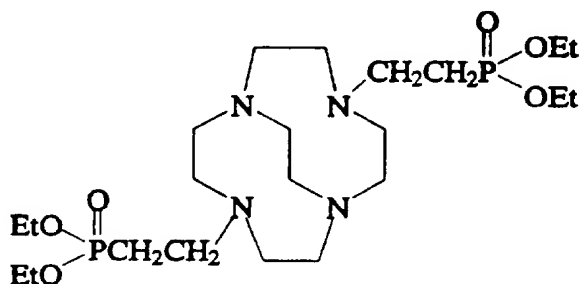
69



1.3.2.12

**1.3.2.13 4,10-Bis(diethylphosphorylethyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) dihydrobromide, potassium carbonate and diethyl(2-bromoethyl)phosphonate (1.2.5.5).

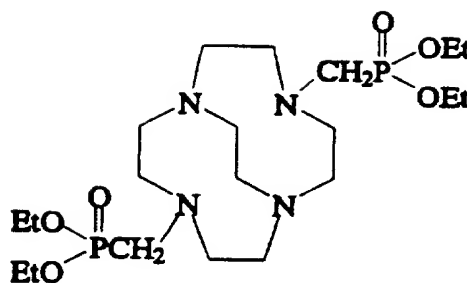


1.3.2.13

**1.3.2.14 4,10-Bis(diethylphosphoryl methyl)-1,4,7,10-tetraazabicyclo [5.5.2] tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) trihydrobromide, formaldehyde and diethylphosphite (commercially available).

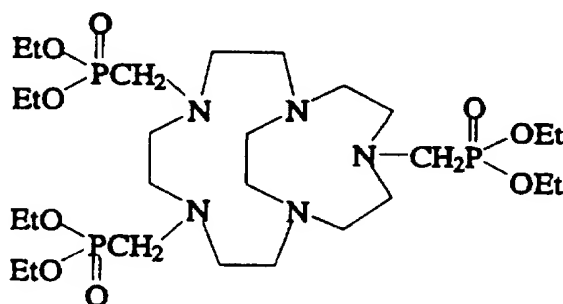
70



1.3.2.14

**1.3.2.15     N,N',N''-Tris(diethylphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane.**

From 1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.1.25), formaldehyde and diethylphosphite (commercially available).



1.3.2.15

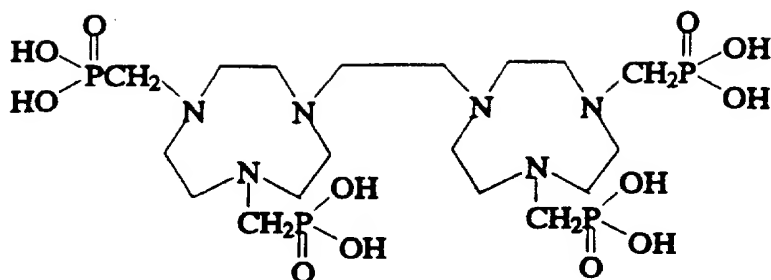
**1.3.3            Synthesis of Polyaza Ligands with Identical Alkylphosphonic Acid Pendant Arms.**

These compounds were prepared by either hydrolizing the ester groups of the compounds described under 1.3.2, or from the polyaza base, formaldehyde and phosphorous acid.

**1.3.3.1            1, 2-Bis(N,N'-bis(dihydroxyphosphrylmethyl)-1,4,7-triazacyclononan-1-yl) ethane.**

From 1,2-bis-(1,4,7-triazacyclononan-1-yl)ethane (1.1.28), formaldehyde and phosphorous acid.

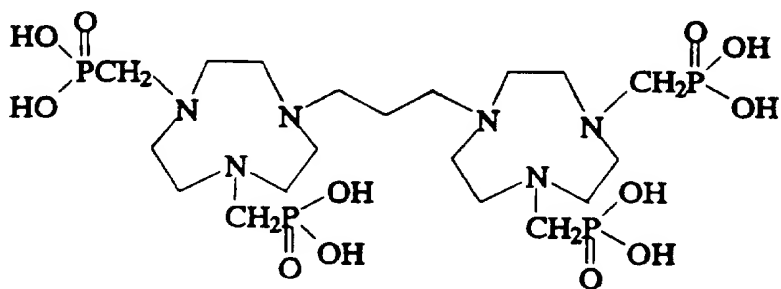
71



1.3.3.1

**1.3.3.2      1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)propane.**

From 1,2-Bis-(1,4,7-triazacyclononan-1-yl)propane (1.1.19), formaldehyde and phosphorous acid.

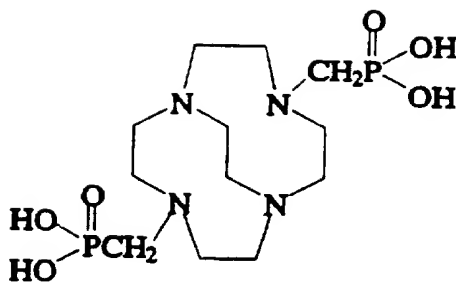


1.3.3.2

**1.3.3.3      4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (1.1.20) trihydrobromide, formaldehyde and phosphorous acid.

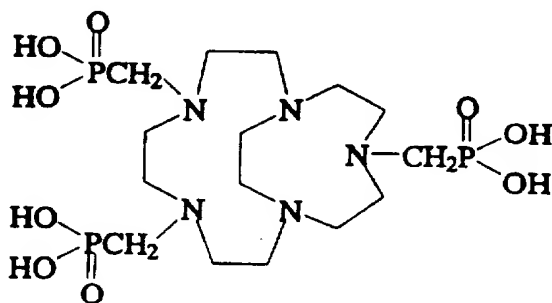
72



1.3.3.3

**1.3.3.4 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane.**

From hydrolysis of 1,4,7,13-tris(diethylphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.2.15) by HCl.

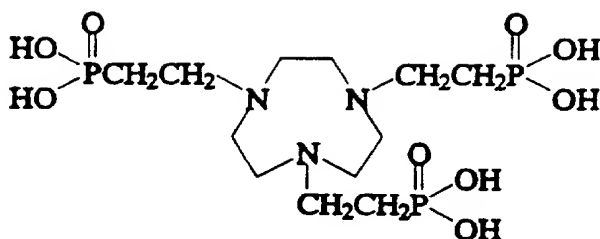


1.3.3.4

The following compounds were prepared from the corresponding diesters by hydrolysis with HCl:

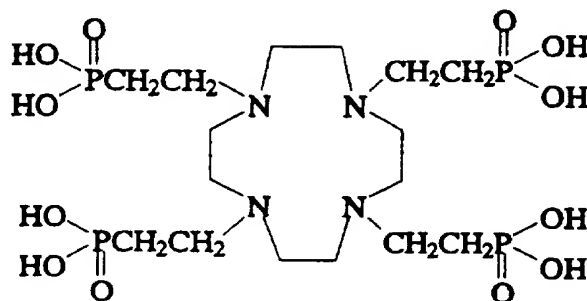
**1.3.3.5 N,N',N''-Tris(dihydroxyphosphorylethyl)-1,4,7-triazacyclononane.**

73



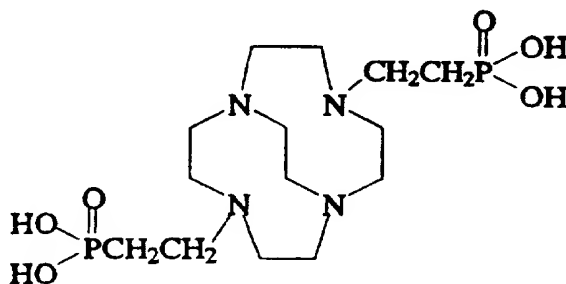
1.3.3.5

**1.3.3.6**      **N,N',N'',N'''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane.**



1.3.3.6

**1.3.3.7**      **4,10-Bis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**



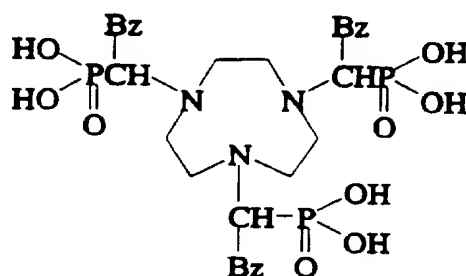
1.3.3.7

### 1.3.4 Synthesis of Polyaza Ligands with Pendant Arms Containing Phosphonate Esters and Acids with Alpha Substituent Groups.

Alkyl or aryl groups  $\alpha$  to the phosphonate moiety were prepared by alkylation of the corresponding ligand in the form of its dialkylphosphonate.

#### 1.3.4.1 N,N',N''-Tris[ $\alpha$ -dihydroxyphosphoryl- $\alpha$ -benzyl)methyl]-1,4,7-Triazacyclononane.

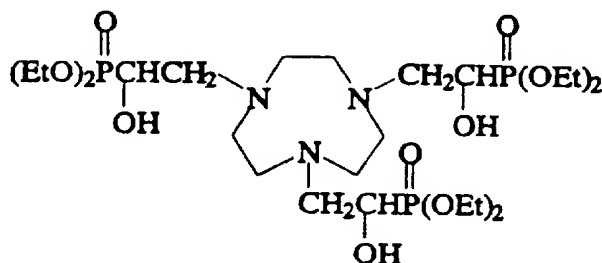
From N,N',N''-Tris[ $\alpha$ -diethylphosphoryl- $\alpha$ -benzyl)methyl]-1,4,7-triazacyclononane (US patent 5,380,515) and trimethylsilyl iodide.



1.3.4.1

#### 1.3.4.2 N,N',N''-Tris{[(diethylphosphoryl)- $\alpha$ -hydroxy]ethyl}-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3) and 2-diethylphosphoryl oxirane (1.2.5.7).

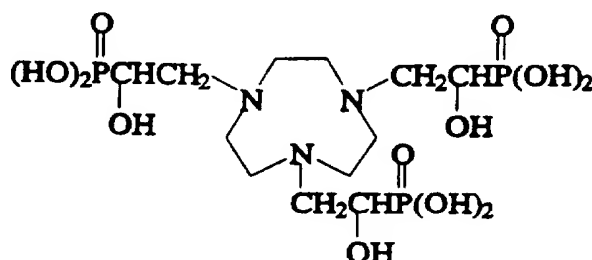


1.3.4.2

75

**1.3.4.3 N,N',N''-Tris[dihydroxyphosphoryl- $\alpha$ -hydroxy]ethyl]-1,4,7-triazacyclononane.**

From 1.3.4.2 and HCl.



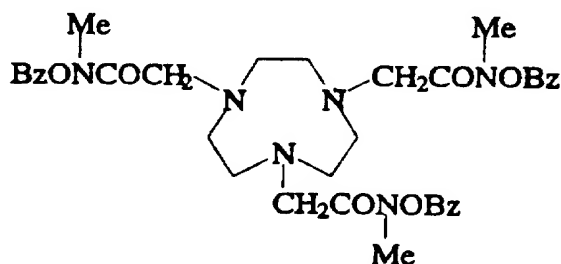
1.3.4.3

**1.3.5 Synthesis of Polyaza Ligands with Pendant Arms Containing Hydroxamate Groups.**

These compounds were prepared by reacting 1,4,7-tetraazacyclononane (1.1.3) trihydrobromide with a N-alkyl-O-benzyl chloroacetohydroxamic acid in the presence of a base. The free hydroxamic acid was obtained by removing the benzyl protecting group by hydrogenolysis.

**1.3.5.1 N,N',N''-Tris[(N-methyl-N-benzyloxycarbamoyl)methyl]1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane, sodium carbonate and O-benzyl-N-methyl chloroacetohydroxamate (1.2.7.1).

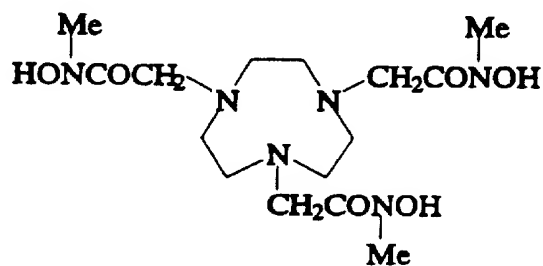


1.3.5.1

76

**1.3.5.2      N,N',N''-Tris[(N-methyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

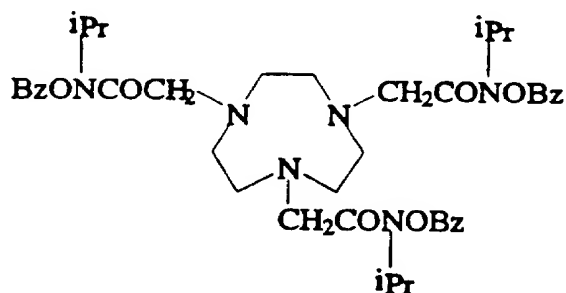
From N,N',N''-Tris[(N-methyl-N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.1) and H<sub>2</sub> and Pd/C.



1.3.5.2

**1.3.5.3      N,N',N''-Tris[(N-isopropyl-N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-Triazacyclononane trihydrobromide and chloroaceto-N-isopropyl-O-benzyl hydroxamate (1.2.7.2).

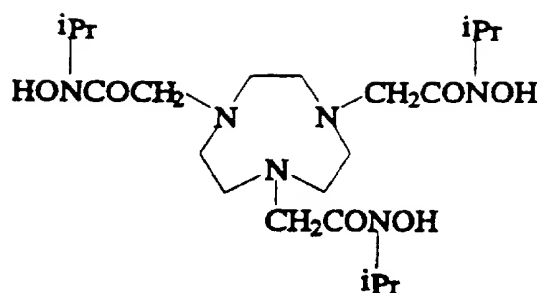


1.3.5.3

**1.3.5.4      N,N',N''-Tris[(N-isopropyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.3 and H<sub>2</sub> and Pd/C.

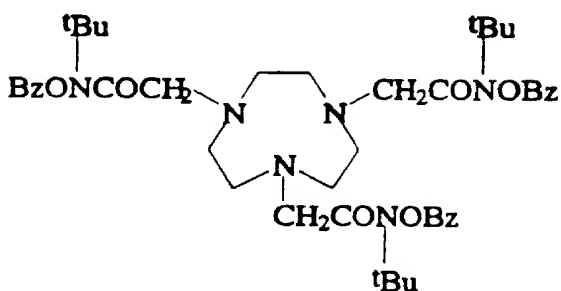
77



1.3.5.4

**1.3.5.5    N,N',N''-Tris[(N-t-butyl-N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane trihydrobromide and chloroaceto-N-t-butyl-O-benzyl hydroxamate (1.2.7.3).

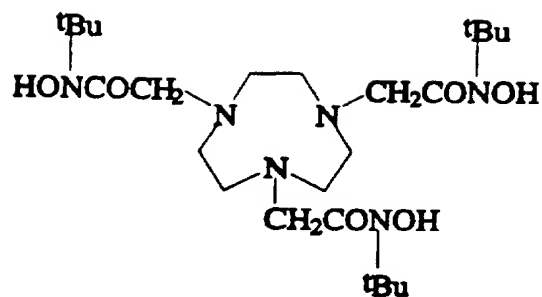


1.3.5.5

**1.3.5.6    N,N',N''-Tris[(N-t-butyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.5, H<sub>2</sub> and Pd/C.

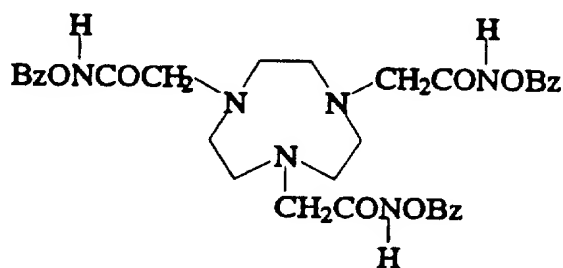
78



1.3.5.6

**1.3.5.7      N,N',N''-Tris[(N-benzyloxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide and chloroaceto-O-benzyl hydroxamate (1.2.7.4).

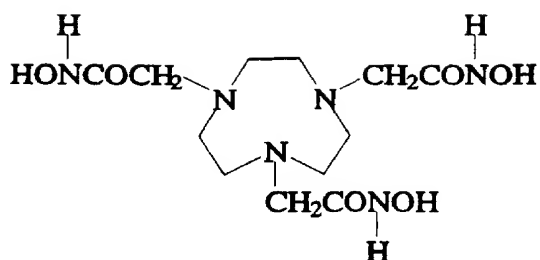


1.3.5.7

**1.3.5.8      N,N',N''-Tris[(N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.7 and H<sub>2</sub> and Pd/C.

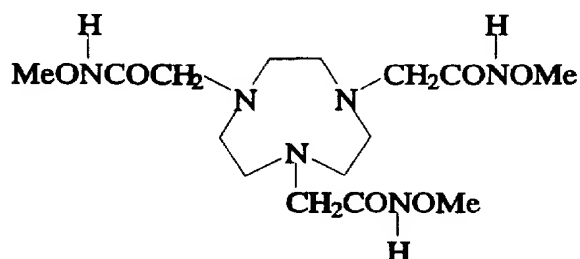
79



1.3.5.8

**1.3.5.9      N,N',N''-Tris[(N-methoxycarbamoyl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3) trihydrobromide and chloroaceto-O-methyl hydroxamate (1.2.7.5).

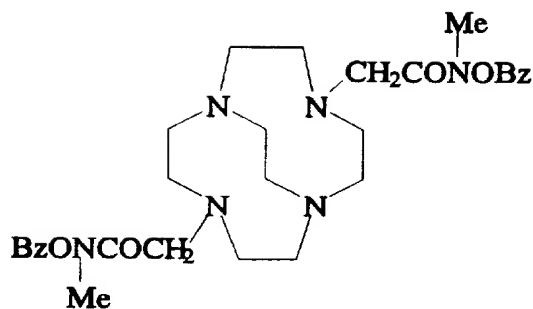


1.3.5.9

**1.3.5.10      4,10-Bis[(N-benzyloxycarbamoyl-N-methyl)methyl]-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) dihydrobromic acid, sodium carbonate and chloroaceto-O-benzyl hydroxamate (1.2.7.4).

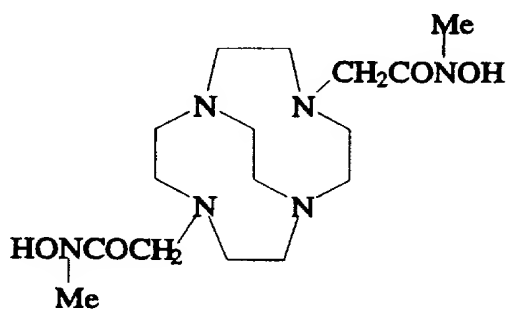
80



1.3.5.10

**1.3.5.11 4,10-Bis[(N-hydroxycarbamoyl-N-methyl)methyl]-1,4,7,10-Tetraazabicyclo [5.5.2] tetradecane.**

From 1.3.5.10 and H<sub>2</sub> and Pd/C.

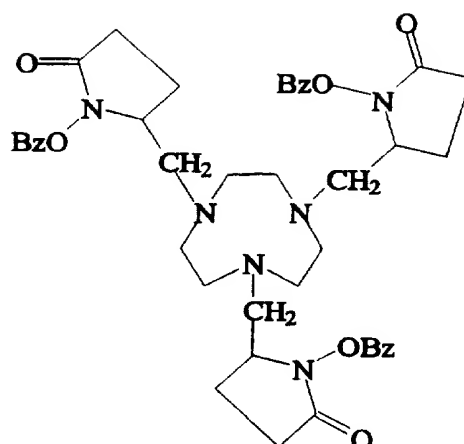


1.3.5.11

**1.3.5.12 N,N',N''-Tris[(1-benzyloxy-2-pyrrolidone-5-yl)methyl]-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), 5-(p-toluenesulfonyloxymethyl)-1-benzyloxy-2-pyrrolidone (1.2.6.3) and base.

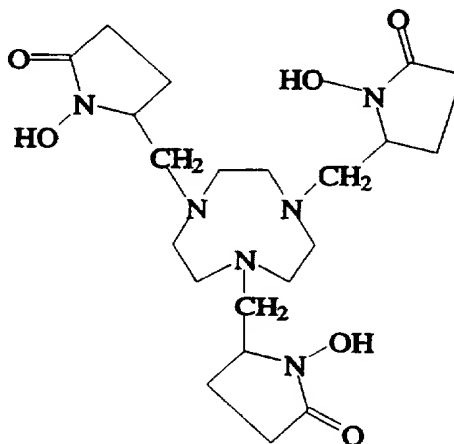
81



1.3.5.12

**1.3.5.13 N,N',N''-Tris[(1-oxy-2-pyrrolidone-5-yl)methyl]-1,4,7-triazacyclononane.**

From 1.3.5.12 and Pd/C (5%) and H<sub>2</sub>.

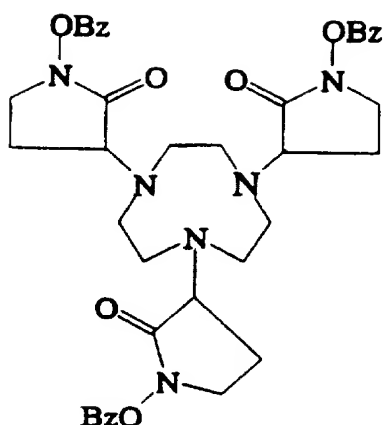


1.3.5.13

**1.3.5.14 N,N',N''-Tris(1-benzyloxy-2-pyrrolidone-5-yl)-1,4,7-triazacyclononane.**

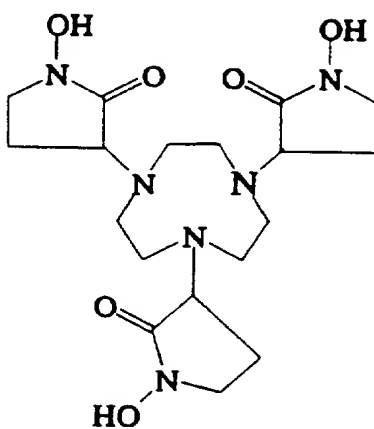
From 1,4,7-triazacyclononane (1.1.3), 5-bromo-1-benzyloxy-2-pyrrolidone (1.2.6.11) and base.

82



1.3.5.14

- 1.3.5.15** ***N,N',N''*-Tris(1-oxy-2-pyrrolidone-5-yl)-1,4,7-triazacyclononane.**  
 From 1.3.5.14 and Pd/C (5%) and H<sub>2</sub>.

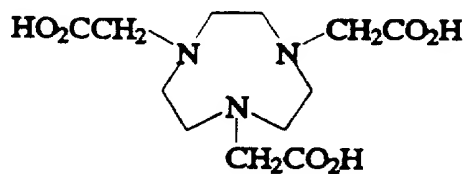


1.3.5.15

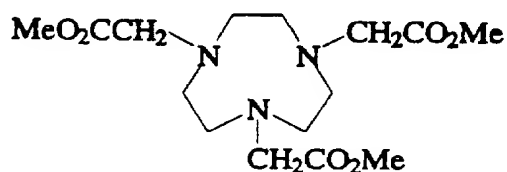
**1.3.6** **Synthesis of Polyaza Ligands with Pendant Arms Containing Carboxyl Groups And The Corresponding Esters.**

Compounds were prepared by reacting polyaza bases with either halo carboxylic acids or by reductive alkylation with aldo or keto acids. The esters were prepared either by reacting directly with halo carboxylic acid esters or by reaction of the free acid with SOCl<sub>2</sub>/alcohol.

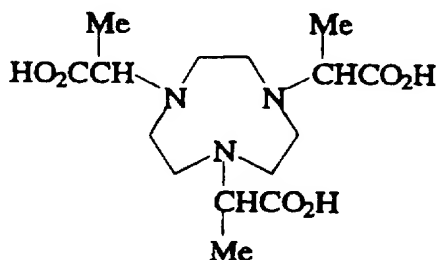
83

**1.3.6.1 N,N',N''-Tris(carboxymethyl)-1,4,7-triazacyclononane.**From 1,4,7-triazacyclononane (1.1.3), glyoxylic acid and H<sub>2</sub>/Pt.

1.3.6.1

**1.3.6.2 N,N',N''-Tris(methoxycarbonylmethyl)-1,4,7-triazacyclononane.**From N,N',N''-tris(carboxymethyl)-1,4,7-triazacyclononane in methanol and SOCl<sub>2</sub>.

1.3.6.2

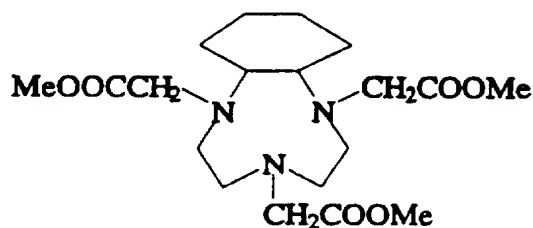
**1.3.6.3 N,N',N''-Tris(α-methylcarboxymethyl)-1,4,7-Triazacyclononane.**From 1,4,7-triazacyclononane (1.1.3), pyruvic acid and H<sub>2</sub>/Pt.

1.3.6.3

**1.3.6.4 N,N',N''-Tris(methoxycarbonylmethyl-1,4,7-triazabicyclo-[7.4.0<sup>8,13</sup>]tridecane.**

From 1,4,7-Triazabicyclo[7.4.0<sup>8,13</sup>]tridecane hydrobromide

5 (1.1.14), glyoxylic acid and H<sub>2</sub>/PtO<sub>2</sub> in methanol.

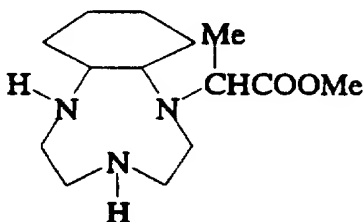


**1.3.6.4**

**1.3.6.5 N-( $\alpha$ -methylcarboxymethyl)-1,4,7-triazabicyclo[7.4.0]tridecane.**

From 1,4,7-triazabicyclo[7.4.0<sup>8,13</sup>]tridecane (1.1.14), pyruvic acid

10 and H<sub>2</sub>/PtO<sub>2</sub>.

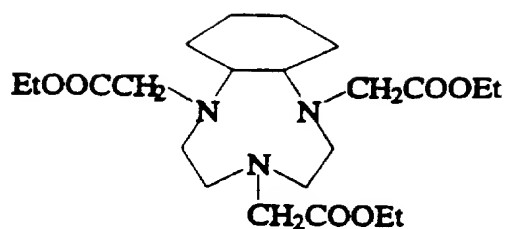


**1.3.6.5**

**1.3.6.6 N,N',N''-Tris(ethoxycarbonylmethyl)-1,4,7-triazabicyclo[7.4.0]tridecane.**

15 From 1,4,7-triazabicyclo[7.4.0<sup>8,13</sup>]tridecane (1.1.14), sodium methoxide and ethyl bromoacetate.

85

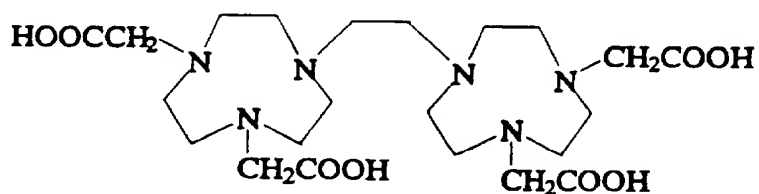


1.3.6.6

**1.3.6.7 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane.**

From 1,2-Bis(1,4,7-triazacyclononan-1-yl)ethane (1.1.28),

5 chloroacetic acid and NaOH.

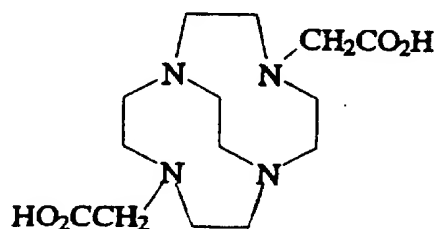


1.3.6.7

**1.3.6.8 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.22),

10 chloroacetic acid and NaOH.

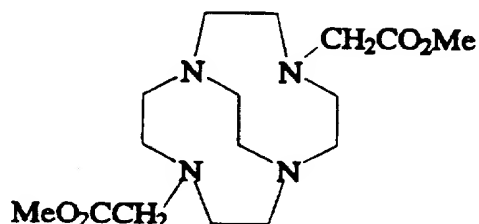


1.3.6.8

86

**1.3.6.9 4,7-Bis(methoxycarbonylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 4,7-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) in MeOH/H<sub>2</sub>SO<sub>4</sub>.

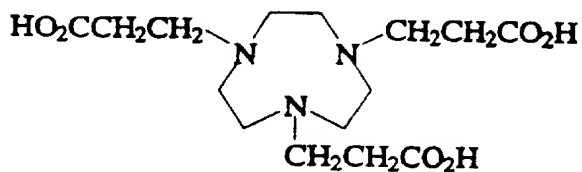


1.3.6.9

5

**1.3.6.10 N,N',N''-Tris(carboxyethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), 3-chloropropionic acid and base.



1.3.6.10

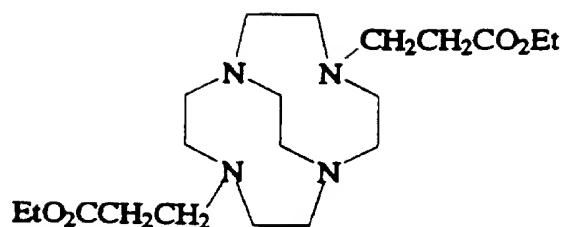
10

**1.3.6.11 4,10-Bis(ethoxycarbonylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20) and ethyl acrylate.

15

87

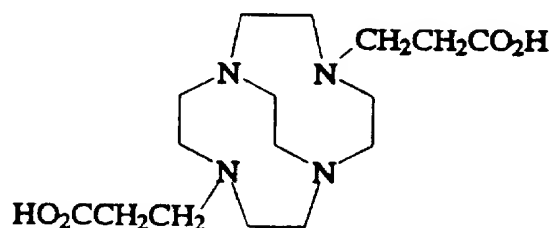


1.3.6.11

**1.3.6.12**     **4,10-Bis(carboxymethyl)-1,4,7,10-**  
**tetraazabicyclo[5.5.2]tetradecane.**

5

From 1.3.6.11 by acid hydrolysis.

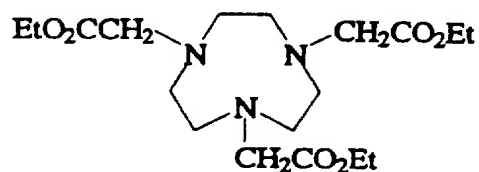


1.3.6.12

**1.3.6.13**     **N,N',N''-Tris(ethoxycarbonylmethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), ethyl bromoacetate and

10     base.

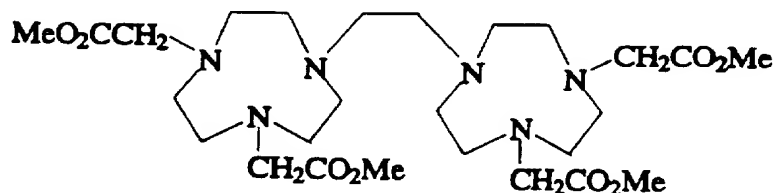


1.3.6.13

88

**1.3.6.14 1,2-Bis-(4,7-methoxycarbonylmethyl-1,4,7-triazacyclononan-1-yl)-ethane.**

From 1,2-bis-(4,7-carboxymethyl-1,4,7-Triazacyclononan-1-yl)ethane (1.3.6.7), MeOH/SOCl<sub>2</sub>.

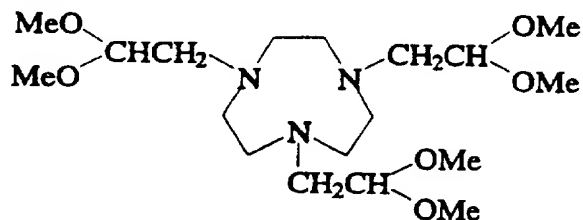


1.3.6.14

5

**1.3.7 Synthesis of Polyaza Ligands with Pendant Arms Containing Aldehyde or Ketone Groups.****1.3.7.1 N,N',N''-Tris(2,2-dimethoxyethyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), 1-chloro-2,2-dimethoxyethane (commercially available) and sodium carbonate.

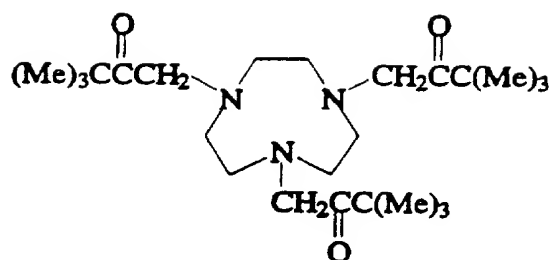


1.3.7.1

**1.3.7.2 N,N',N''-Tris-(3,3-dimethyl-2-oxo-butyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), bromomethyl t-butyl ketone (commercially available) and sodium carbonate.

89

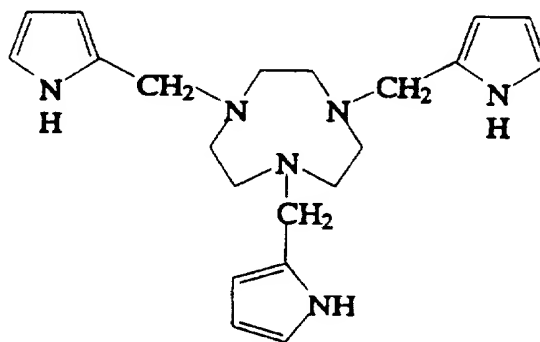


1.3.7.2

1.3.8 SYNTHESIS OF POLYAZA LIGANDS WITH PENDANT ARMS  
5 CONTAINING PYRROLE GROUPS.

1.3.8.1 N,N',N''-Tris(-pyrrol-2-yl-methyl)-1,4,7-triazacyclononane.

From 1,4,7-triazacyclononane (1.1.3), pyrrole-2-carboxaldehyde (commercially available) and  $H_2/PtO_2$ .

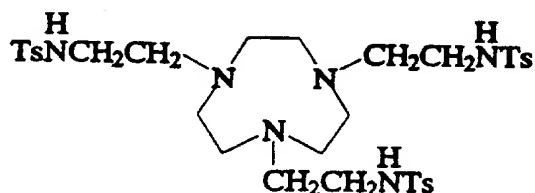


1.3.8.1

10

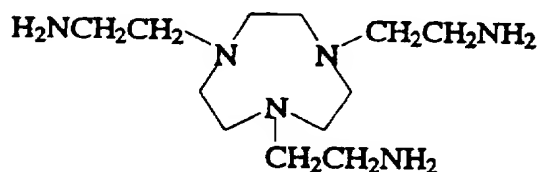
### 1.3.9 SYNTHESIS OF POLYAZA LIGANDS WITH PENDANT ARMS CONTAINING AMINE GROUPS.

- 5 1.3.9.1 **N,N',N''-Tris(2-p-toluenesulfonyloxyethyl)-1,4,7-triazacyclononane.**  
From 1,4,7-triazacyclononane (1.1.3), 2-(p-toluenesulfonylamino)-1-(p-toluenesulfonyloxy)ethane (1.1.16) and base.



#### 1.3.9.1

- 10 1.3.9.2 **N,N',N''-Tris(2-aminoethyl)-1,4,7-triazacyclononane.**  
From 1.3.9.1 and HBr/acetic acid.



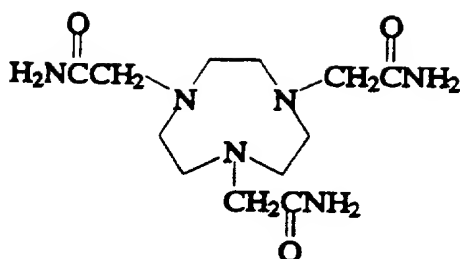
#### 1.3.9.2

- 15 1.3.10 **Synthesis of Polyaza Ligands with Pendant Arms Containing Amide Groups.**

1.3.10.1 **N,N',N''-Tris(methylcarboxamide)-1,4,7-triazacyclononane.**

- From N,N',N''-Tris-(methoxycarbonylmethyl)-1,4,7-triazacyclononane (1.3.6.2) and ammonia.
- 20

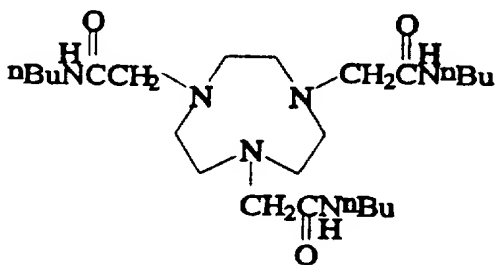
91



1.3.10.1

**1.3.10.2 N,N',N''-Tris[(-N-n-butyl(methylcarboxamide))-1,4,7-triazacyclononane.**

5 From N,N',N''-Tris-(methoxycarbonylmethyl)-1,4,7-triazacyclononane (1.3.6.2) and butylamine.



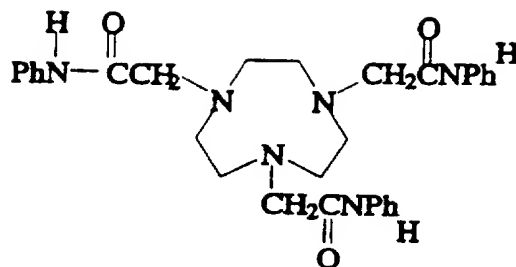
1.3.10.2

**1.3.10.3 N,N',N''-Tris[(-N-n-phenyl(methylcarboxamide))-1,4,7-triazacyclononane.**

10

From 1,4,7-triazacyclononane (1.1.3), N-phenylchloroacetamide (prepared from aniline and chloroacetyl chloride) and excess sodium carbonate.

92

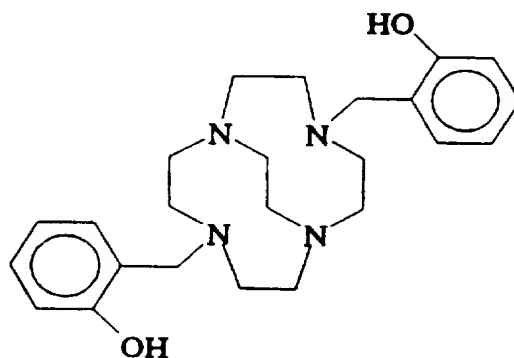


1.3.10.3

**1.3.11 Synthesis of Polyaza Ligands with Pendant Arms Containing Phenolic Groups.**

**1.3.11.1 4,7-Di-(2-hydroxy-benzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20),  
salicylaldehyde (excess) and  $H_2/PtO_2$ .

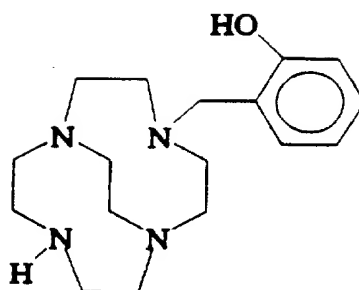


1.3.11.1

**1.3.11.2 4-(2-hydroxy-benzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.20),  
salicylaldehyde (1.5 equivalents) and  $H_2/PtO_2$ .

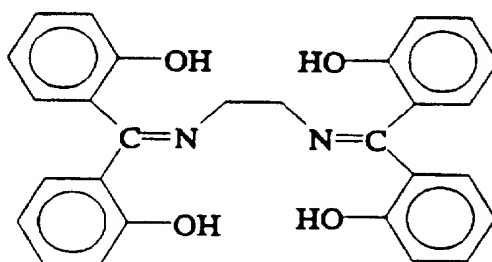
93



1.3.11.2

**1.3.11.3 Bis-(2,2'-dihydroxybiphenylmethylene) ethylene diamine.**

From ethylenediamine (1.1.0) and 2,2'-dihydroxy benzophenone  
 5 (commercially available) with removal of H<sub>2</sub>O.

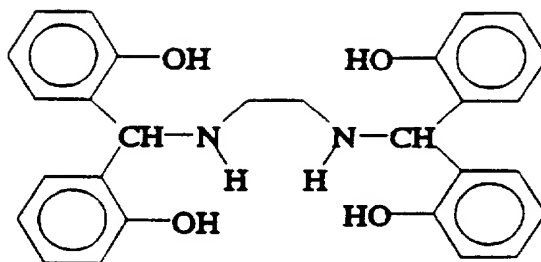


1.3.11.3

**1.3.11.4 N,N'-Bis-(2,2'-dihydroxybiphenylmethyl) ethylene diamine.**

From 1.3.11.3 and sodium borohydride.

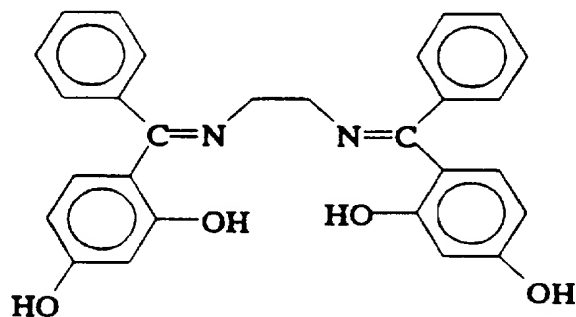
94



1.3.11.4

**1.3.11.5 Bis-(2,4-dihydroxybiphenylmethylene) ethylenediamine.**

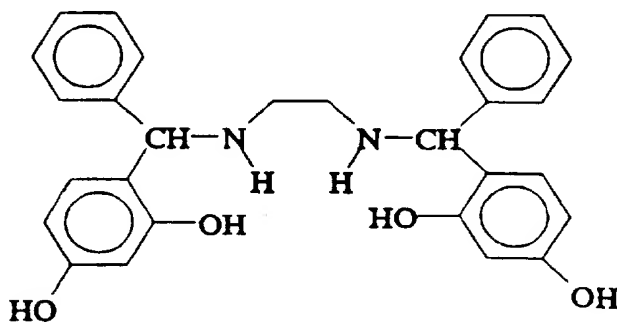
From ethylenediamine (1.1.0) and 2,4-dihydroxy benzophenone

5 (commercially available) with removal of H<sub>2</sub>O.

1.3.11.5

**1.3.11.6 N,N'-Bis-(2,4-dihydroxybiphenylmethyl) ethylenediamine.**

From 1.3.11.5 and sodium borohydride.

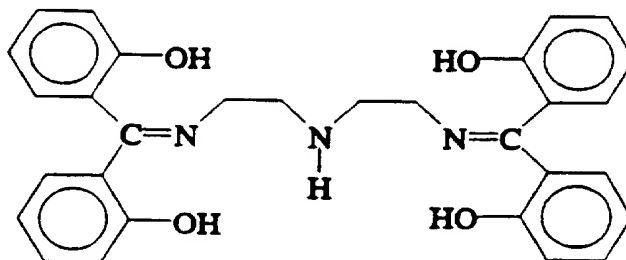


1.3.11.6

95

**1.3.11.7 N,N''-Bis-(2,2'-dihydroxybiphenylmethylene) diethylene triamine.**

From diethylene triamine (1.1.1) and 2,2'-dihydroxy benzophenone with removal of H<sub>2</sub>O.

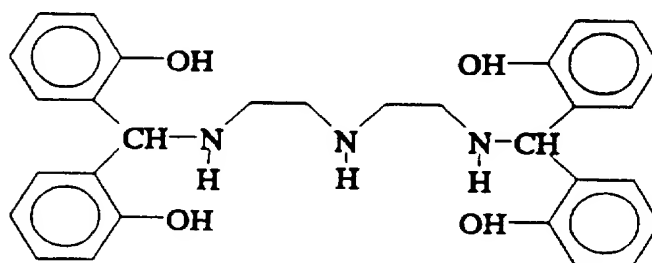


1.3.11.7

5

**1.3.11.8 N,N''-Bis-(2,2'-dihydroxybiphenylmethyl) diethylene triamine.**

From 1.3.11.7 and sodium borohydride.

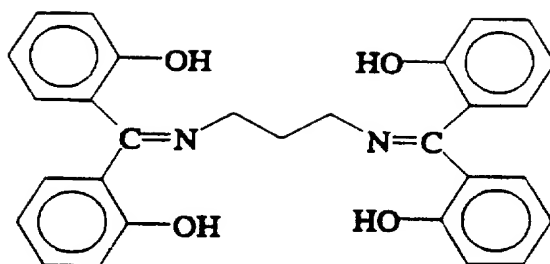


1.3.11.8

**10 1.3.11.9 Bis-(2,2'-dihydroxybiphenylmethylene)-1,3-diaminopropane.**

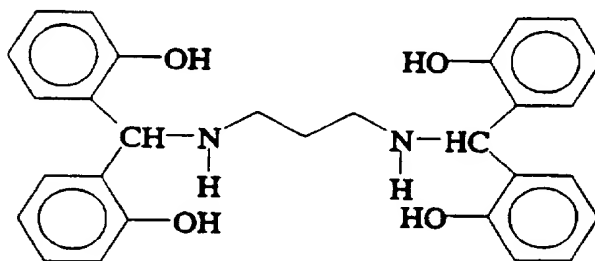
From diaminopropane and 2,2'-dihydroxy benzophenone with removal of H<sub>2</sub>O.

96



1.3.11.9

- 1.3.11.10 N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)-1,3-diaminopropane.**  
From and 1.3.11.9 and sodium borohydride.

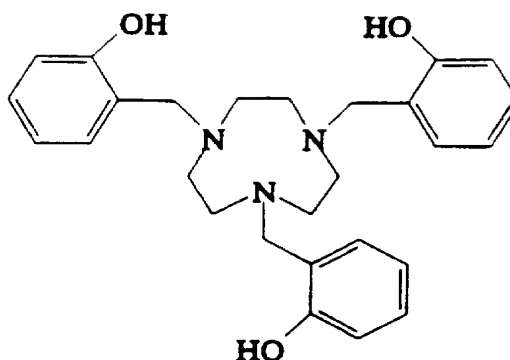


1.3.11.10

5

- 1.3.11.11 N,N',N''-Tris(2-hydroxybenzyl)-1,4,7-triazacyclononane.**  
From 1,4,7-triazacyclononane, salicylaldehyde and  $H_2/PtO_2$ .

97



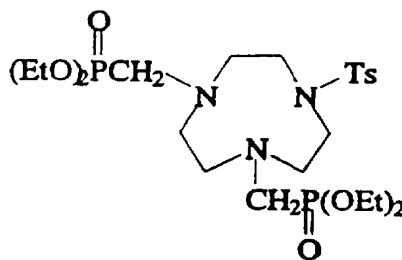
1.3.11.11

### 1.3.12 Synthesis of Polyaza Ligands with More Than One Species of Pendant Arm.

5

#### 1.3.12.1 N-(p-Toluenesulfonyl)-N', N''-bis(diethylphosphorylmethyl)-1,4,7-triazacyclononane.

From N-(p-toluenesulfonyl)-1,4,7-triazacyclononane dihydrobromide  
 10 (1.3.13.31), formaldehyde and diethyl phosphite.

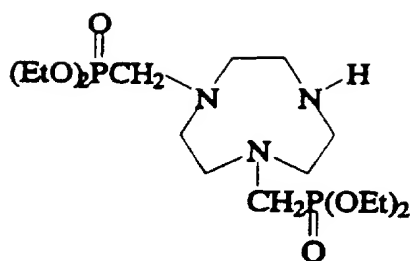


1.3.12.1

#### 1.3.12.2 N,N'-Bis(diethylphosphorylmethyl)-1,4,7-triazacyclononane.

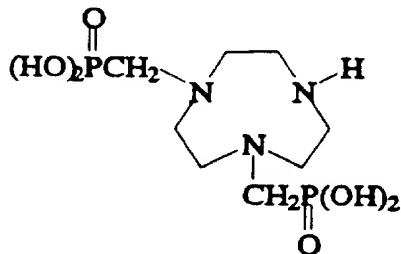
From 1,4,7-triazacyclononane (1.1.3) trihydrobromide, one  
 15 equivalent formaldehyde and one equivalent of diethyl phosphite. Purification of  
 product by chromatography.

98.



1.3.12.2

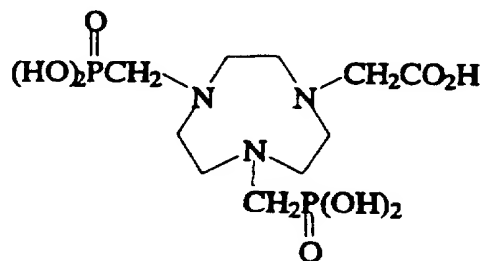
- 1.3.12.3** **N,N'-Bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane.**  
From 1.3.12.2 and HCl.



1.3.12.3

5

- 1.3.12.4** **N-(Carboxymethyl)-N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane.**  
From 1.3.12.3, chloroacetic and NaOH.



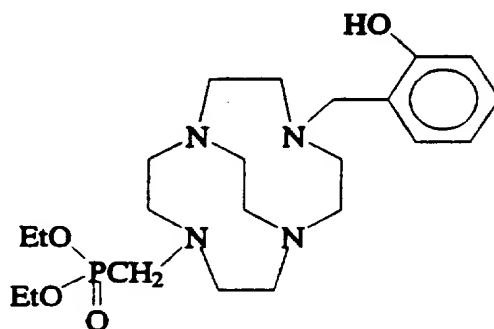
1.3.12.4

10

99

**1.3.12.5 4-(2-Hydroxy-benzyl)-7-diethylphosphorylethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 4-(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.2), diethyl phosphite and  
5 formaldehyde solution.

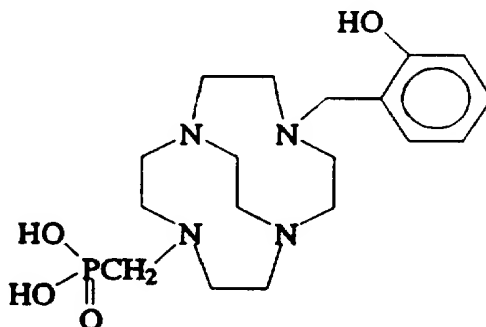


1.3.12.5

**1.3.12.6 4-(2-hydroxy-benzyl)-7-phosphorylethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

10

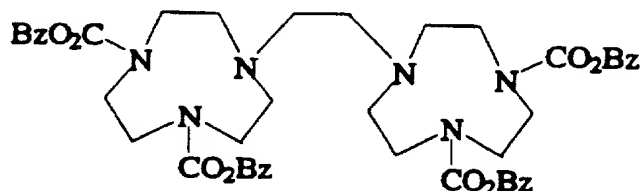
From 1.3.12.5 and HCl.



1.3.12.6

**1.3.13 Miscellaneous Substituted Polyaza Compounds.****1.3.13.1 1,2-Bis-(4,7-benzyloxycarbonyl-1,4,7-triazacyclononan-1-yl)ethane.**

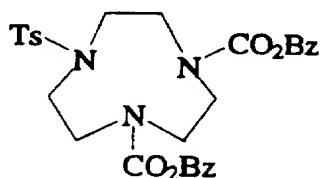
From 1,2-bis-(1,4,7-triazacyclononan-1-yl)ethane(1.1.28)  
polyhydrobromide, potassium carbonate and benzyl chloroformate.

**1.3.13.1**

5

**1.3.13.2 N-(p-Toluenesulfonyl)-N',N''-Bis-(benzyloxycarbonyl)-1,4,7-triazacyclononane.**

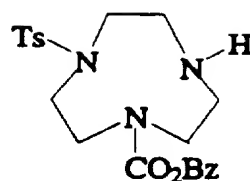
From N-(p-toluenesulfonyl)-1,4,7-triazacyclononane dihydrobromide  
(1.3.13.31),  $K_2CO_3$  and benzyl chloroformate.

**1.3.13.2****1.3.13.3 N-(p-Toluenesulfonyl)-N''-benzyloxycarbonyl-1,4,7-triazacyclononane.**

From N-(p-toluenesulfonyl)-N',N''-bis(benzyloxycarbonyl)-1,4,7-triazacyclononane (1.3.13.2) and trimethylsilyl iodide.

15

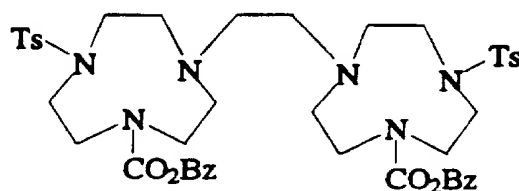
101



1.3.13.3

**1.3.13.4 1,2-Bis[(1-p-toluenesulfonyl)-4-benzyloxycarbonyl-1,4,7-triazacyclonon-7-yl]ethane.**

5 From 1-(p-toluenesulfonyl)-4-benzyloxycarbonyl-1,4,7-triazacyclononane (1.3.13.3), potassium carbonate and dibromoethane.

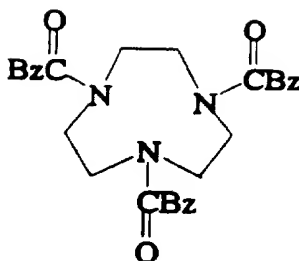


1.3.13.4

**1.3.13.5 N,N',N''-Tris(phenylacetyl)-1,4,7-triazacyclononane.**

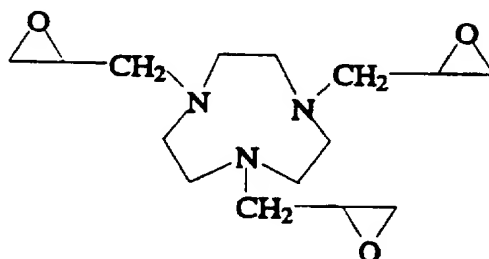
10 From 1,4,7-triazacyclononane (1.1.3), diethyl phenylacetylphosphonate [PhCH<sub>2</sub>COP(O)(OEt)<sub>2</sub>].

102



1.3.13.5

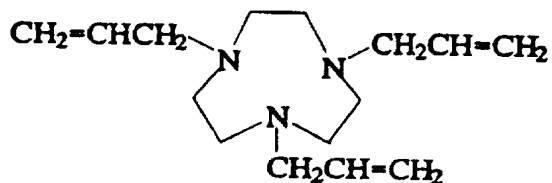
- 1.3.13.6** **N,N',N''-Tris(2,3-Epoxypropyl)-1,4,7-Triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3) and epibromohydrin.



1.3.13.6

5

- 1.3.13.7** **N,N',N''-Tri-allyl-1,4,7-triazacyclononane.**  
 From 1,4,7-triazacyclononane (1.1.3), sodium hydride and allyl  
 bromide.



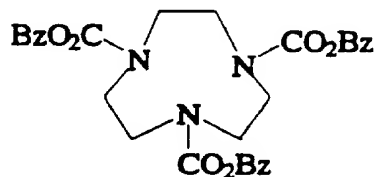
1.3.13.7

10

103

**1.3.13.8 N,N',N''-Tris(benzyloxycarbonyl)-1,4,7-triazacyclononane.**

From 1,4,7-triazacyclononane (1.1.3), benzyl chloroformate and sodium carbonate.

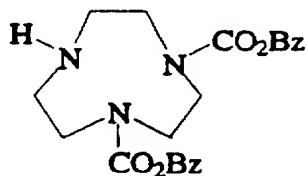


1.3.13.8

5

**1.3.13.9 N,N'-Bis(benzyloxycarbonyl)-1,4,7-triazacyclononane.**

From N,N',N''-tris(benzyloxycarbonyl)-1,4,7-triazacyclononane (1.3.13.8) and iodotrimethylsilane.



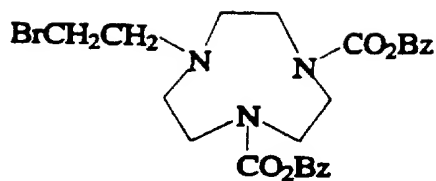
1.3.13.9

10

**1.3.13.10 N,N'-Bis(benzyloxycarbonyl)-N''-(2-bromoethyl)-1,4,7-triazacyclononane.**

From N,N'-bis(benzyloxycarbonyl)-1,4,7-triazacyclononane (1.3.13.9), dibromoethane and potassium carbonate.

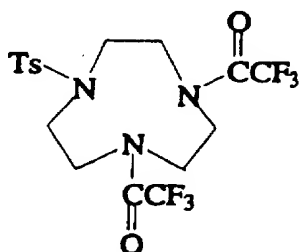
104



1.3.13.10

**1.3.13.11 N-p-Toluenesulfonyl-N',N''-ditrifluoroacetyl-1,4,7-triazacyclononane.**

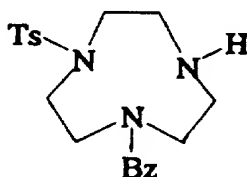
5 From N-p-toluenesulfonyl-1,4,7-triazacyclononane (1.3.13.31), potassium carbonate and trifluoroacetic anhydride.



1.3.13.11

**1.3.13.12 N-p-Toluenesulfonyl-N'-benzyl-1,4,7-triazacyclononane.**

10 From N-(p-toluenesulfonyl-1,4,7-triazacyclononane (1.3.13.31), sodium hydride and benzyl bromide.

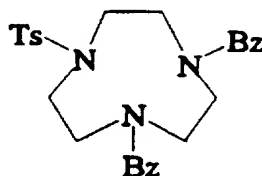


1.3.13.12

105

**1.3.13.13 N-p-Toluenesulfonyl-N',N"-dibenzyl-1,4,7-triazacyclononane.**

From N-(p-toluenesulfonyl-1,4,7-triazacyclononane (1.3.13.31), sodium hydride and benzyl bromide.

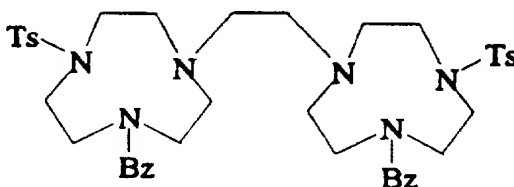


1.3.13.13

5

**1.3.13.14 1,2-Bis(N-p-toluenesulfonyl-N'-benzyl)-1,4,7-triazacyclononan-1-yl) ethane.**

From N-p-toluenesulfonyl-N'-benzyl-1,4,7-triazacyclononane (1.3.13.12), dibromoethane and potassium carbonate.



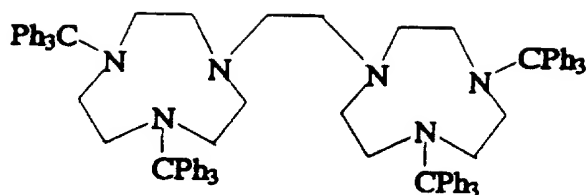
1.3.13.14

10

**1.3.13.15 1,2-Bis(N,N'-ditrityl-1,4,7-triazacyclononan-1-yl)ethane.**

From 1,2-Bis(1,4,7-triazacyclononane)ethane (1.1.28), potassium carbonate and trityl chloride.

106

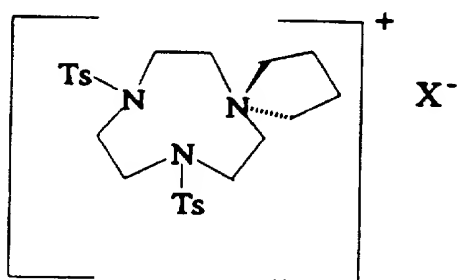


1.3.13.15

**1.3.13.16 Spiro [4,8]-4,7-di-p-toluenesulfonyl-4,7-diaza-1-azotridecane halide.**

From 1,4,7-triazacyclononane-N,N'-di-p-toluenesulfonyl

5 hydrobromide (1.3.13.32), diiodobutane and potassium carbonate.

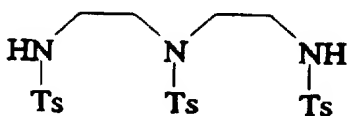


1.3.13.16

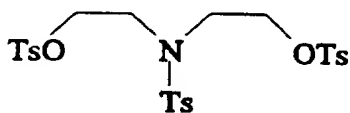
**1.3.13.17 Tetrakis(p-toluenesulfonyl)-1,4,7,10-tetraazacyclotetradecane.**

From N,N',N''-tris(p-toluenesulfonyl)diethylenetriamine (1.3.13.18),

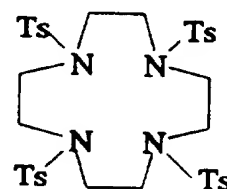
10 potassium carbonate and bis(2-p-toluenesulfonyloxyethyl)-N-(p-toluenesulfonyl) amine (1.3.13.19).



1.3.13.18



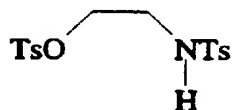
1.3.13.19



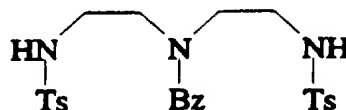
1.3.13.17

**1.3.13.20 1,7-Bis(p-toluenesulfonyl)-4-benzyl-1,4,7-triazaheptane.**

From benzylamine, (2-p-toluenesulfonyloxy)-N-(p-toluenesulfonyl)-ethylamine (1.3.13.21) and potassium carbonate.



1.3.13.21

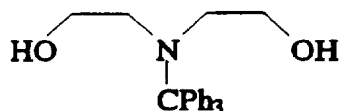


1.3.13.20

5

**1.3.13.22 N-Trityldiethanolamine.**

From diethanolamine and trityl chloride.

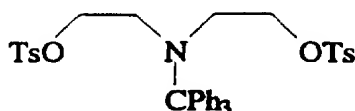


1.3.13.22

10

**1.3.13.23 N-Trityl-bis(2-p-toluenesulfonyloxyethyl)amine.**

From N-trityldiethanolamine and p-toluenesulfonyl chloride.



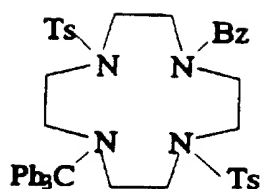
1.3.13.23

15

**1.3.13.24 1,7-di-(p-toluenesulfonyl)-4-benzyl-10-trityl-1,4,7,10-tetraazacyclotetradecane.**

From 1,7-di-p-toluenesulfonyl-4-benzyl-1,4,7-triazaheptane (1.3.13.20), sodium hydride and N-trityl-di-p-toluenesulfonyldiethanolamine (1.3.13.23).

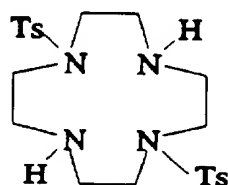
108



1.3.13.24

**1.3.13.25** 1,7-Di-(p-toluenesulfonyl)-1,4,7,10-tetraazacyclotetradecane.

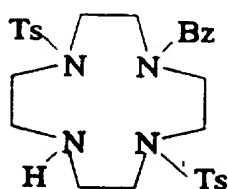
From 1,7-di-(p-toluenesulfonyl)-4-benzyl-10-trityl-1,4,7,10-tetraazacyclotetradecane (1.3.13.24) reduced by  $H_2$  and Pd/C.



1.3.13.25

**1.3.13.26** 1,7-Di-(p-toluenesulfonyl)-4-benzyl-1,4,7,10-tetraazacyclotetradecane.

From reduction of 1.3.13.24.

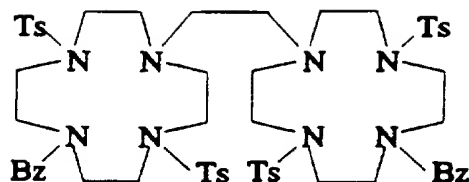


1.3.13.26

**1.3.13.27** 1,2-Bis-(4,10-di-p-toluenesulfonyl-7-benzyl-1,4,7,10-tetraazacyclotetradecan-1-yl)ethane.

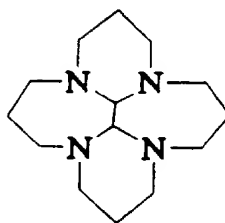
From 1.3.13.26 and dibromoethane.

109



1.3.13.27

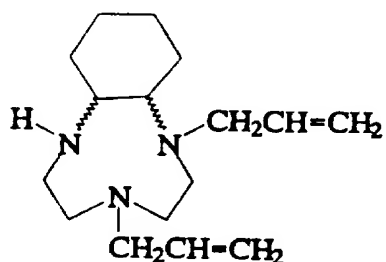
- 1.3.13.28** 1,5,9,13-Tetraazatetracyclo[6,6,2,0<sup>1,15</sup>, 0<sup>8,16</sup>]hexadecane  
From 1.1.6 and glyoxaldehyde.



1.3.13.28

5

- 1.3.13.29** 4,7-Diallyl-1,4,7-triazabicyclo[7,4,0]tridecane.  
From 1,4,7-triazabicyclo[7,4,0]tridecane trihydrobromide (1.1.14),  
sodium hydride and allyl bromide.



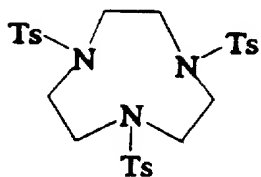
1.3.13.29

10

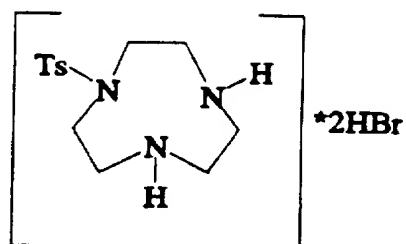
110

**1.3.13.30 N-p-Toluenesulfonyl-1,4,7-triazacyclononane dihydrobromide.**

From N,N',N''-Tris(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.3.13.31) prepared from 1.3.13.18, dibromoethane and base) and HBr/acetic acid.



1.3.13.31

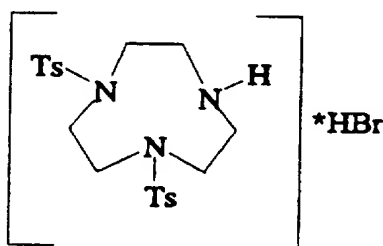


1.3.13.30

5

**1.3.13.32 N,N'-Di-p-Toluenesulfonyl-1,4,7-triazacyclononane hydrobromide.**

a) From N,N',N''-tris(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.3.13.31) and HBr/acetic acid as the hydrobromide salt.

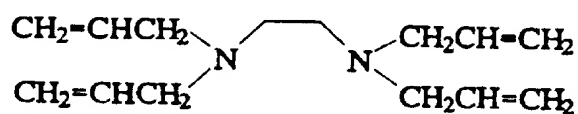


1.3.13.32

10

**1.3.13.33 N,N,N',N'-Tetraallylethylenediamine.**

From ethylenediamine, sodium carbonate and allyl bromide.

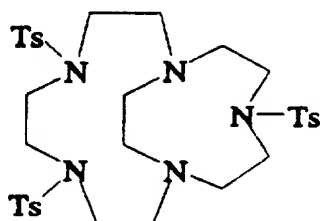


1.3.13.33

15

**1.3.13.34 4,7,13-Tris(p-toluenesulfonyl)-1,4,7,10-13-pentaazabicyclo[8.5.2]heptadecane.**

From 1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.1.26), potassium carbonate and p-toluenesulfonyl chloride.

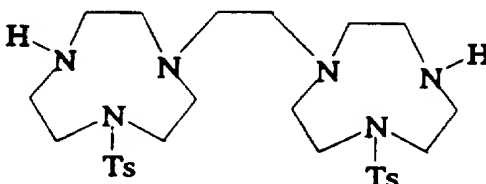


1.3.13.34

5

**1.3.13.35 1,2-Bis(4-p-toluenesulfonyl-1,4,7-triazacyclonon-1-yl)ethane.**

From 1,2-bis(4,7-di-p-toluenesulfonyl-1,4,7-triazacyclonon-1-yl)ethane (1.1.30) and sulphuric acid.



1.3.13.35

10

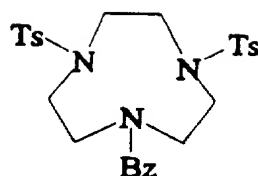
**1.3.13.36 N,N'-(Di-p-toluenesulfonyl)-N''-benzyl-1,4,7-Triazacyclononane.**

a) From N,N''-(p-toluenesulfonyl)-4-benzyl diethylenetriamine (1.3.13.20), sodium hydride and ethylene glycol di-p-toluenesulfonate (1.1.12).

b) From N,N'-bis(p-toluenesulfonyl)-1,4,7-triazacyclononane (1.3.13.32), sodium hydride and benzyl bromide.

15

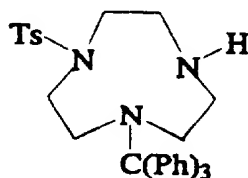
112



1.3.13.36

**1.3.13.37 N-(p-Toluenesulfonyl)-N'-trityl-1,4,7-triazacyclononane.**

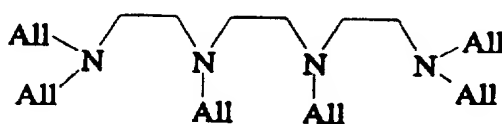
From N-(p-toluenesulfonyl-1,4,7-triazacyclononane dihydrobromide  
 5 (1.3.13.30), sodium hydride and trityl chloride.



1.3.13.37

**1.3.13.38 Hexakis(allyl) triethylenetetramine.**

From triethylenetetramine (1.1.2), sodium carbonate and allyl  
 10 bromide.

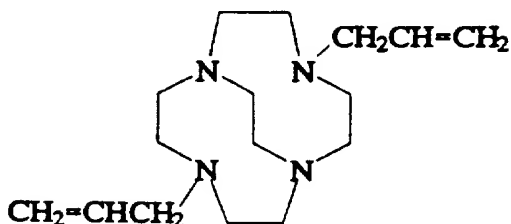


1.3.13.38

113

**1.3.13.39 4,7-diallyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane.**

From 1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.1.4), allyl bromide and base.



1.3.13.39

5

**EXAMPLE 2**

This example illustrates the preparation of metal complexes using the chelating agents (ligands) described in Example 1.

10

**2.1 Synthesis of Metal Complexes**

Water soluble salts of metals and compounds described in the above examples were heated in water or alcohol solvents followed by base addition to neutral or basic pH. Alternately, an excess of these metals in the form of their corresponding insoluble oxides or hydroxides was heated with the acid form of the compounds described in preceding sections until complexation was complete, followed by filtration to remove uncomplexed excess metal oxide or hydroxide. In either case complex formation was verified by chromatography. Employing these methods the following complexes were synthesized:

20

**2.1.1 Iron (III) complexes with the following Compounds:**

**2.1.1.1. 1,2-Bis(1,4,7-triazabicyclononan-1-yl)ethane (1.1.29)**

**2.1.1.2. N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.1)**

5 **2.1.1.3. (R, R, R) N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.2).**

**2.1.1.4. (S, S, S) N,N',N"-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.3).**

10 **2.1.1.5. N,N',N"-Tris(2-hydroxy-3-isobutoxypropyl)-1,4,7-triazacyclononane (1.3.1.4).**

**2.1.1.6. (R, R, R) N,N',N"-Tris(2-hydroxy-3-isobutoxypropyl)-1,4,7-triazacyclononane (1.3.1.5).**

**2.1.1.7. N,N',N"-Tris(2-hydroxy-3-methoxypropyl)-1,4,7-triazacyclononane (1.3.1.6).**

15 **2.1.1.8. N,N',N"-Tris(2,3-dihydroxypropyl)-1,4,7-triazacyclononane (1.3.1.7).**

**2.1.1.9. N,N',N"-Tris(2-hydroxy-3-allyloxypropyl)-1,4,7-triazacyclononane (1.3.1.9).**

20 **2.1.1.10. N,N',N"-Tris(2-hydroxy-3-phenoxypropyl)-1,4,7-triazacyclononane (1.3.1.10 ).**

**2.1.1.11. N,N',N"-Tris(2-hydroxy-2,2-diethoxymethylene)ethyl-1,4,7-triazacyclononane (1.3.1.11).**

**2.1.1.12. N,N',N"-Tris(2-hydroxy-2,2-dimethoxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.12).**

25 **2.1.1.13. N,N',N"-Tris(2-hydroxy-2,2-diisopropoxyloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).**

**2.1.1.14. N,N',N"-Tris[2-hydroxy-bis(2-furfurylmethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.14).**

30 **2.1.1.15. N,N',N"-Tris(3-hydroxy-1,5-dioxacycloheptyl-3-methyl)-1,4,7-triazacyclononane (1.3.1.15 ).**

**2.1.1.16. N,N',N"-Tris[(3-Hydroxy-7,7-dimethyl-1,5-dioxacyclooct-3-yl)-methyl]-1,4,7-triazacyclononane (1.3.1.16).**

- 2.1.1.17. N,N',N"-Tris[(3-hydroxy-7-methyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.17).
- 2.1.1.18. N,N',N"-Tris[(3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-Triazacyclononane (1.3.1.18).
- 5 2.1.1.19. N,N',N"-Tris[(3-hydroxy-benzo[b]-1,5-dioxacycloheptyl)methyl]1,4,7-triazacyclononane (1.3.1.19).
- 2.1.1.20. N,N',N"-Tris[(3-hydroxy-1,5-dioxacyclooctan-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.20).
- 2.1.1.21. N,N',N"-Tris[(4-fluoro-2-hydroxy-3-isopropyl-4-methyl)pentyl]-1,4,7- triazacyclononane (1.3.1.22).
- 10 2.1.1.22. N,N',N"-Tris-[2-hydroxy-3-(1-fluoroethyl)-4-hydroxypentyl]-1,4,7-triazacyclononane (1.3.1.23).
- 2.1.1.23. N,N',N"-Tris[2-hydroxy-2-(1-fluoroethyl)-2-(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.24).
- 15 2.1.1.24. N,N',N"-Tris(2-hydroxy-2-ethyl-3-methoxybutyl)-1,4,7-triazacyclononane (1.3.1.25).
- 2.1.1.25. N,N',N"-Tris[(2,3-dihydroxy-2-ethyl)butyl]-1,4,7-triazacyclononane (1.3.1.26).
- 2.1.1.26. N,N',N"-Tris[2-hydroxy-2,2-bis(1-fluoroethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.27).
- 20 2.1.1.27. N,N',N"-Tris[2-hydroxy-2,2-bis(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.28).
- 2.1.1.28. N,N',N"-Tris[(3,3-dimethyl-2-hydroxy)butyl]-1,4,7-triazacyclononane (1.3.1.29).
- 25 2.1.1.29. N,N',N"-Tris(2-hydroxycyclohexan-1-yl)-1,4,7-triazacyclononane (1.3.1.33).
- 2.1.1.30. N,N',N",N"'-Tetrakis(2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclotetradecane (1.3.1.38).
- 2.1.1.31. 4,10-Bis(2-hydroxypropyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.1.39).
- 30 2.1.1.32. 4,10-Bis-(2-hydroxyethyl)-1,4,7,10-tetrazabicyclo[5.5.2]tetradecane (1.3.1.40).

- 2.1.1.33. 4,10-Bis-(2,3-dihydroxypropyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.1.42).
- 2.1.1.34. N,N',N"-Tris[(2,4-dihydroxy-3-isopropyl-4-methyl)pentyl]-1,4,7-triazacyclononane (1.3.1.54).
- 5 2.1.1.35. N,N',N"-Tris(2-hydroxy-bis(2,2-dihydroxymethyl)ethyl)-1,4,7-triazacyclononane (1.3.1.55).
- 2.1.1.36. N,N',N"-Tris(dihydroxyphosphoryl mono butyl ester)methyl-1,4,7-triazacyclononane (1.3.2.2).
- 2.1.1.37. N,N',N"-Tris(dihydroxyphosphorylmethyl monoethyl ester)-  
10 1,4,7-triazacyclononane (1.3.2.4).
- 2.1.1.38. N,N',N"-Tris(dihydroxyphosphorylmethyl monoethyl ester)-1,4,7-triazacyclononane (1.3.2.6).
- 2.1.1.39. N,N',N"-Tris(dihydroxyphosphorylmethyl monoisobutyl ester)-1,4,7-triazacyclononane (1.3.2.8).
- 15 2.1.1.40. 1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)ethane (1.3.3.1).
- 2.1.1.41. 1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)propane (1.3.3.2).
- 2.1.1.42. 4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane.  
20
- 2.1.1.43. 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.3.4).
- 2.1.1.44. N,N',N"-Tris(dihydroxyphosphorylethyl)-1,4,7-triazacyclononane (1.3.3.5).
- 25 2.1.1.45. N',N'',N''',N''''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane (1.3.3.6).
- 2.1.1.46. 4,10-Bis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.3.7).
- 2.1.1.47. N,N',N"-Tris[(N-methyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.2).  
30
- 2.1.1.48. N,N',N"-Tris[(N-isopropyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.4).

- 2.1.1.49. N,N',N"-Tris[(N-t-butyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.6).
- 2.1.1.50. N,N',N"-Tris[(N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.8).
- 5 2.1.1.51. N,N',N"-Tris[(N-methoxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.9).
- 2.1.1.52. 4,10-Bis[(N-hydroxy-N-methylcarbamoyl)methyl]-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.5.11).
- 2.1.1.53. N,N',N"-Tris[(1-hydroxy-2-pyrrolidon-5-yl)methyl]-1,4,7-triazacyclononane (1.3.5.13).
- 10 2.1.1.54. N,N',N"-Tris[(1-hydroxy-2-pyrrolidon-5-yl)methyl]-1,4,7-triazacyclononane (1.3.5.13).
- 2.1.1.55. N,N',N"-Tris(carboxymethyl)-1,4,7-triazacyclononane (1.3.6.1).
- 2.1.1.56. 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).
- 15 2.1.1.57. N,N',N"-Tris(carboxyethyl)-1,4,7-triazacyclononane (1.3.6.10).
- 2.1.1.58. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).
- 2.1.1.59. N,N',N"-Tris(2,2-dimethoxyethyl)-1,4,7-triazacyclononane (1.3.7.1).
- 20 2.1.1.60. N,N',N"-Tris(pyrrol-2-yl-methyl)-1,4,7-triazacyclononane (1.3.8.1).
- 2.1.1.61. N,N',N"-Tris[N-n-butyl(carbamoylmethyl)]-1,4,7-triazacyclononane (1.3.10.2).
- 2.1.1.62. N,N',N"-Tris[N-phenyl(carbamoylmethyl)]-1,4,7-triazacyclononane (1.3.10.3).
- 25 2.1.1.63. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.1.1.64. N,N'-Bis-(2,4-dihydroxybiphenylmethyl)ethylenediamine (1.3.11.6).
- 2.1.1.65. N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)diethylenetriamine (1.3.11.8).
- 30 2.1.1.66. N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)-1,3-diaminopropane (1.3.11.10).

2.1.1.67. **N,N',N"-Tris(2-hydroxybenzyl)-1,4,7-triazacyclononane (1.3.11.11).**

2.1.1.68. **N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-Triazacyclononane (1.3.12.3).**

5 2.1.1.69. **N-(carboxymethyl)-N',N"-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (1.3.12.4).**

2.1.2 **Gadolinium (III) complexes with the following chelators:**

10 2.1.2.1. **1,2-Bis(N,N'-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononan-1-yl)ethane (1.3.1.13).**

2.1.2.2. **1,2-Bis(N,N'-bis(dihydroxyphosphrylmethyl)-1,4,7-triazacyclononan-1-yl)propane (1.3.3.2).**

15 2.1.2.3. **4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.3.4).**

2.1.2.4. **N,N',N", N'''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane (1.3.3.6).**

2.1.2.5. **N,N',N"-Tris[2-dihydroxyphosphoryl-1-hydroxy)ethyl]-1,4,7-triazacyclononane (1.3.4.3).**

20 2.1.2.6. **1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).**

2.1.2.7. **N,N'-Bis-(2,2'-dihydroxybiphenylmethyl)ethylenediamine (1.3.11.4).**

2.1.2.8. **N,N'-Bis-(2,4-dihydroxybiphenylmethyl)ethylenediamine (1.3.11.6).**

25

2.1.3 **Copper (II) complexes with the following Compounds:**

2.1.3.1. **1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (1.1.22).**

30 2.1.3.2. **N,N',N"-Tris(2-hydroxy-2,2-diisopropyloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).**

2.1.3.3. **4,10-Bis(2-Hydroxypropyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.1.39).**

- 2.1.3.4. 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).
- 2.1.3.5. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).
- 5 2.1.3.6. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.1.4 Zinc (II) complexes with the following Compounds:
- 10 2.1.4.1. N,N',N''-Tris(2-hydroxy-2,2-diisopropylloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).
- 2.1.4.2. 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).
- 2.1.4.3. 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).
- 15 2.1.4.4. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.1.5 Manganese (II) complexes with the following Compounds:
- 20 2.1.5.1. 4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.3.3).
- 2.1.5.2. 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo [8.5.2]heptadecane (1.3.3.4).
- 25 2.1.5.3. 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).
- 2.1.5.4. 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).

**2.1.6 Cadmium (II) complexes with the following Compounds:**

**2.1.6.1 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (1.3.3.4).**

**2.1.7 Lead (II) complexes with the following Compounds:**

**2.1.7 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo [8.5.2]heptadecane (1.3.3.4).**

**2.1.8 Mercury (II) complexes with the following Compounds:**

**2.1.8.1 4,7,13-Tris(dihydroxyphosphorylmethyl)-1,4,7,10,13-pentaazabicyclo [8.5.2]heptadecane (1.3.3.4).**

**2.1.9 Nickel (II) complexes with the following Compounds:**

**2.1.9.1 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).**

**2.1.10 Calcium (II) complexes with the following Compounds:**

**2.1.10.1 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).**

**2.1.10.2 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).**

**2.1.11 Magnesium (II) complexes with the following Compounds:**

**2.1.11.1 4,10-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.12).**

**2.1.11.2. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).**

## **2.2 Synthesis of Radioactive Complexes**

5 Water soluble salts of radioisotopes of iron(III) and gadolinium or manganese (II) (*e.g.*, chloride salts of Fe-59, Gd-153) and chelators described in Examples 1.3 were heated in water, alcohol or DMSO solvents followed by base addition to achieve neutral or basic pH. Complex formation was verified by radiochromatography. Employing this method the following complexes were  
10 synthesized.

### **2.2.1 Complexes of Fe-59**

- 15 **2.2.1.1. N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.1).**
- 2.2.1.2. (R, R, R) N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.2).**
- 2.2.1.3. (S, S, S) N,N',N''-Tris(2-hydroxy-3-isopropoxypropyl)-1,4,7-triazacyclononane (1.3.1.3).**
- 20 **2.2.1.4. (R, R, R) N,N',N''-Tris(2-hydroxy-3-isobutoxypropyl)-1,4,7-triazacyclononane (1.3.1.5).**
- 2.2.1.5. N,N',N''-Tris(2-hydroxy-3-methoxypropyl)-1,4,7-triazacyclononane (1.3.1.6).**
- 25 **2.2.1.6. N,N',N''-Tris(2,3-dihydroxypropyl)-1,4,7-triazacyclononane (1.3.1.7).**
- 2.2.1.7. N,N',N''-Tris(2-hydroxy-2,2-diisopropoxyloxymethyl)ethyl-1,4,7-triazacyclononane (1.3.1.13).**
- 2.2.1.8. N,N',N''-Tris(3-hydroxy-1,5-dioxacycloheptyl-3-methyl)-1,4,7-triazacyclononane (1.3.1.15).**
- 30 **2.2.1.9. N,N',N''-Tris[(3-hydroxy-7,7-dimethyl-1,5-dioxacyclooct-3-yl)-methyl]-1,4,7-triazacyclononane (1.3.1.16).**

- 2.2.1.10. **N,N',N''-Tris[(3-hydroxy-6,6,7,7-tetramethyl-1,5-dioxacyclohept-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.18).**
- 2.2.1.11. **N,N',N''-Tris[(3-hydroxy-1,5-dioxacyclooctane-3-yl)methyl]-1,4,7-triazacyclononane (1.3.1.20).**
- 5 2.2.1.12. **N,N',N''-Tris(2-hydroxy-2-methylpropyl)-1,4,7-triazacyclononane (1.3.1.21).**
- 2.2.1.13. **N,N',N''-Tris[(2,3-dihydroxy-2-ethylbutyl)]-1,4,7-triazacyclononane (1.3.1.26).**
- 10 2.2.1.14. **N,N',N''-Tris[2-hydroxy-2,2-bis(1-methoxyethyl)ethyl]-1,4,7-triazacyclononane (1.3.1.28).**
- 2.2.1.15. **N,N',N''-Tris(2-hydroxypropyl)-1,4,7-triazacyclononane (1.3.1.30).**
- 2.2.1.16. **N,N',N''-Tris(dihydroxyphosphorylmethyl monobutyl ester)-1,4,7-triazacyclononane (1.3.2.2).**
- 15 2.2.1.17. **N,N',N''-Tris(dihydroxyphosphorylmethyl monoethyl ester)-1,4,7-triazacyclononane (1.3.2.4).**
- 2.2.1.18. **4,10-Bis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.3.3).**
- 2.2.1.19. **N,N',N''-Tris(dihydroxyphosphorylethyl)-1,4,7-triazacyclononane (1.3.3.5).**
- 20 2.2.1.20. **N,N',N'',N'''-Tetrakis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazacyclododecane (1.3.3.6).**
- 2.2.1.21. **4,10-Bis(dihydroxyphosphorylethyl)-1,4,7,10-tetraazabicyclo[5.5.2] tetradecane (1.3.3.7).**
- 2.2.1.22. **N,N',N''-Tris{[(diethylphosphoryl)- $\alpha$ -hydroxy]ethyl}-1,4,7-triazacyclononane (1.3.4.2).**
- 25 2.2.1.23. **N,N',N''-Tris[(N-methyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.2).**
- 2.2.1.24. **N,N',N''-Tris[(N-isopropyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.4).**
- 30 2.2.1.25. **N,N',N''-Tris[(N-t-butyl-N-hydroxycarbamoyl)methyl]-1,4,7-triazacyclononane (1.3.5.6).**

- 2.2.1.26. 1,2-Bis-(4,7-carboxymethyl-1,4,7-triazacyclononan-1-yl)ethane (1.3.6.7).
- 2.2.1.27. N,N',N"-Tris(carboxyethyl)-1,4,7-triazacyclononane (1.3.6.10).
- 2.2.1.28. N,N',N"-Tris[N-n-butyl(methylcarboxamide)]-1,4,7-  
5 triazacyclononane (1.3.10.2).
- 2.2.1.29. 4,7-Bis(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.11.1).
- 2.2.1.30. N,N'-Bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (1.3.12.3).
- 10 2.2.1.31. N-(carboxymethyl)-N',N"-bis(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (1.3.12.4).
- 2.2.2 Complexes of Mn-54
- 15 2.2.2.1 4,7-Bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (1.3.6.8).

### EXAMPLE 3

20 This example illustrates the ability of the chelating agents described above to inhibit cell replication *in vitro*.

#### 3.1: INHIBITION OF BACTERIAL REPLICATION

25 This example demonstrates the ability of a representative example of the claimed ligands to inhibit replication of various bacteria *in vitro*.

N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695. Studies were performed to determine its ability to inhibit bacterial growth. For *Streptococcus hemolyticus*, *Listeria monocytogenes*, *Enterobacter cloacae* and  
30 *Klebsiella pneumoniae* the minimum inhibitory concentration was determined to be 0.15mM/L. For *Enterococcus faecalis*, *Pseudomonas aeruginosa* and

*Acinobacter anitratus* the minimum inhibitory concentration was determined to be 0.3mM/L.

### 3.2: INHIBITION OF MYCOTIC CELL REPLICATION IN VITRO

5 This example demonstrates the ability of a representative example of the claimed ligands to inhibit mycotic (fungal) cell replication *in vitro*.

N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695. Studies were performed to determine its ability to inhibit growth of mycotic (fungal) organisms.

10 For *Microsporum canis* the minimum inhibitory concentration was 0.233 mM/L or less. For *Candida albicans* and *Trichophyton rubrum* the minimal inhibitory concentration was 2.33 mM/L. For *Trichophyton mentagrophytes*, *Trichophyton tonsuras* and *Trichophyton violaceum* the  
15 minimal inhibitory concentration was 23.3 mM/L.

### 3.3: INHIBITION OF MAMMALIAN CELL REPLICATION IN VITRO

This example demonstrates the ability of representative examples of the claimed ligands to inhibit mammalian cell replication *in vitro*.

20 N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7- triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695.

Concentrations of this ligand of 0.009 mM/L inhibited the growth of both BGM cells (a continuous cell line of monkey origin) and HFF cells (human foreskin fibroblasts).

25 N,N',N"-Tris(carboxymethyl)-1,4,7-Triazacyclononane (Example 1.3.6.1) at a concentration of 0.009 mM/L inhibited BGM cell growth and a concentration of 0.019 mM/L inhibited HFF cell growth.

N,N',N"-Tris(ethoxycarbonylmethyl)-1,4,7-Triazacyclononane (Example 1.3.6.13) at a concentration of 0.04 mM/L inhibited BGM cell growth  
30 and at a concentration of 0.16 mM/L inhibited HFF cell growth. Diethylene triamine penta acetic acid at a concentration of 0.075 mM/L inhibited BGM cell growth and at 0.3 mM/L inhibited HFF cell growth.

**EXAMPLE 4**

This example demonstrates the relative lack of toxicity of a representative example of the claimed ligands toward nonproliferating mammalian cells *in vitro*.

N,N',N''-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane was prepared as described in Example 1C in U.S. Patent No. 5,236,695.

A concentration of 0.3mM of this agent was added to mature, nonreplicating cultures of HFF (human foreskin fibroblasts) kept in maintenance media and no effect on the resting cells was observed over a five-day period of observation.

**EXAMPLE 5**

This example illustrates the low *in vivo* toxicity of a representative ligand administer intravenously to mice.

Over 50% of mice receiving 4.0mM/kg intravenously of the sodium salt of N,N',N''-tris-(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane (Example 1C in U.S. Patent No. 5,236,695) as a single intravenous dose survived for over 14 days following such administration demonstrating that the acute LD50 of this agent is in excess of 4mM/kg. This *in vivo* LD50 toxicity dose results in an instantaneous *in vivo* concentration which is orders of magnitude greater than the dose of this agent which inhibits mammalian cell replication *in vitro* (0.009mM/L).

**EXAMPLE 6**

This example demonstrates the relatively low subacute toxicity of a representative ligand administered intravenously in repeated doses to rats.

Ten male Sprague Dawley rats 29 days old and weighing between 73.4 and 87.8 grams at the beginning of the experiment were randomized, employing the block stratification method, into two groups consisting of five

rats each. On each of days 1, 2, 3, 6, 7, 8, 9, 10, 13 and 14 of the experiment one set of rats received an intravenous dose of N,N',N"-tris(dihydroxyphosphorylmethyl)-1,4,7- triazacyclononane (Example 1C in U.S. Patent No. 5,236,695) equal to 0.05 millimoles per kg of initial body weight (experimental group) while the other group received an equivalent volume of normal saline solution. The weights of the animals were recorded three times per week and the animals were sacrificed on the 28th day, major organs removed and weighed and tissues removed for microscopic examination. There was no statistically significant difference in weight or rate of weight gain between the experimental and control group of rats, either during the period of injections or in the two-week post-injection period. There were no differences observed between the weights of major organs of the experimental vs. the control group. There were no differences between the tissues of the experimental vs. the control group upon microscopic examination of the tissues obtained at the time of necropsy.

### EXAMPLE 7

This example illustrates the *in vivo* distribution of radioisotopic complexes

Examples of the *in vivo* distribution of radioisotopic complexes of representative ligands are herein disclosed which demonstrate the ability of these agents to be predominantly excreted by the kidneys, or the liver, or to pass across cell membranes and accumulate in the intracellular fluid space (e.g. in heart muscle). Those skilled in the art will recognize that a similar *in vivo* distribution can be anticipated from non-radioisotopic paramagnetic complex species.

In the following examples certain radioisotopic complexes of the subject ligands were administered intravenously to mice and the tissue distribution of the radioisotopic complexes was measured by detection of radioisotopic content of tissues removed at necropsy.

**6.1: EXAMPLE OF A COMPLEX WHICH IS PREDOMINANTLY EXCRETED BY THE KIDNEYS IN THE URINE**

The iron-59 labeled complex of N,N',N'-tris(2,3-dihydroxy propyl)-1,4,7-triazacyclononane (Example 2.2.1.6) was administered intravenously to mice and at necropsy the tissue distribution of radioactivity showed predominant concentration of the agent in the kidneys and urine.

**6.2: EXAMPLE OF A COMPLEX WHICH IS PREDOMINANTLY EXCRETED BY THE LIVER IN THE BILE.**

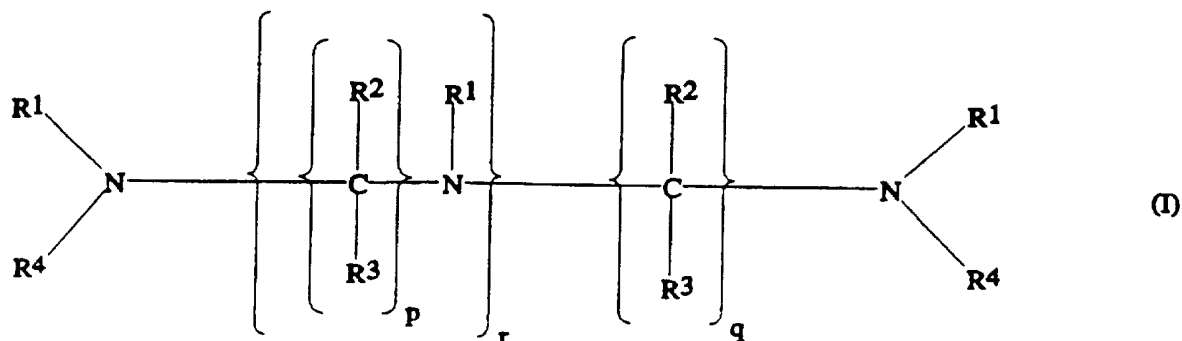
The iron-59 complex of N,N',N"- tris(2'-hydroxy-3-iso-propoxypropyl)-1,4,7-triazacyclononane (Example 2.2.1.1) was administered intravenously to mice and at necropsy the tissue distribution of radioactivity showed predominant concentration of the agent in the liver, bile and intestinal contents.

**6.3: EXAMPLE OF A COMPLEX WHICH RAPIDLY PASSES ACCROSS CELL MEMBRANES AND ENTERS THE INTRACELLULAR FLUID SPACE**

The iron-59 complex of N,N',N"-tris[2-hydroxy-(2,2-diisopropoxy)methyl]ethyl]-1,4,7-triazacyclononane (Example 2.2.1.7) was administered intravenously to mice and at necropsy the tissue distribution of activity was consistent with an intracellular as well as extracellular fluid distribution. Within the first five minutes following agent administration the concentration of activity in the heart was greater than that of mixed venous blood indicating rapid equilibration of the agent across myocardial cell membranes. The liver concentrated the agent and excreted it into the bile.

**WHAT IS CLAIMED IS:**

1. A method for inhibiting bacterial or fungal growth on a surface or in a solution comprising administering to said surface or solution a complexing agent having the formula:



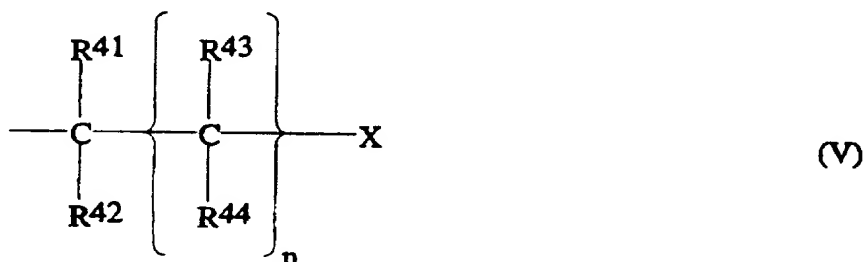
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



wherein,

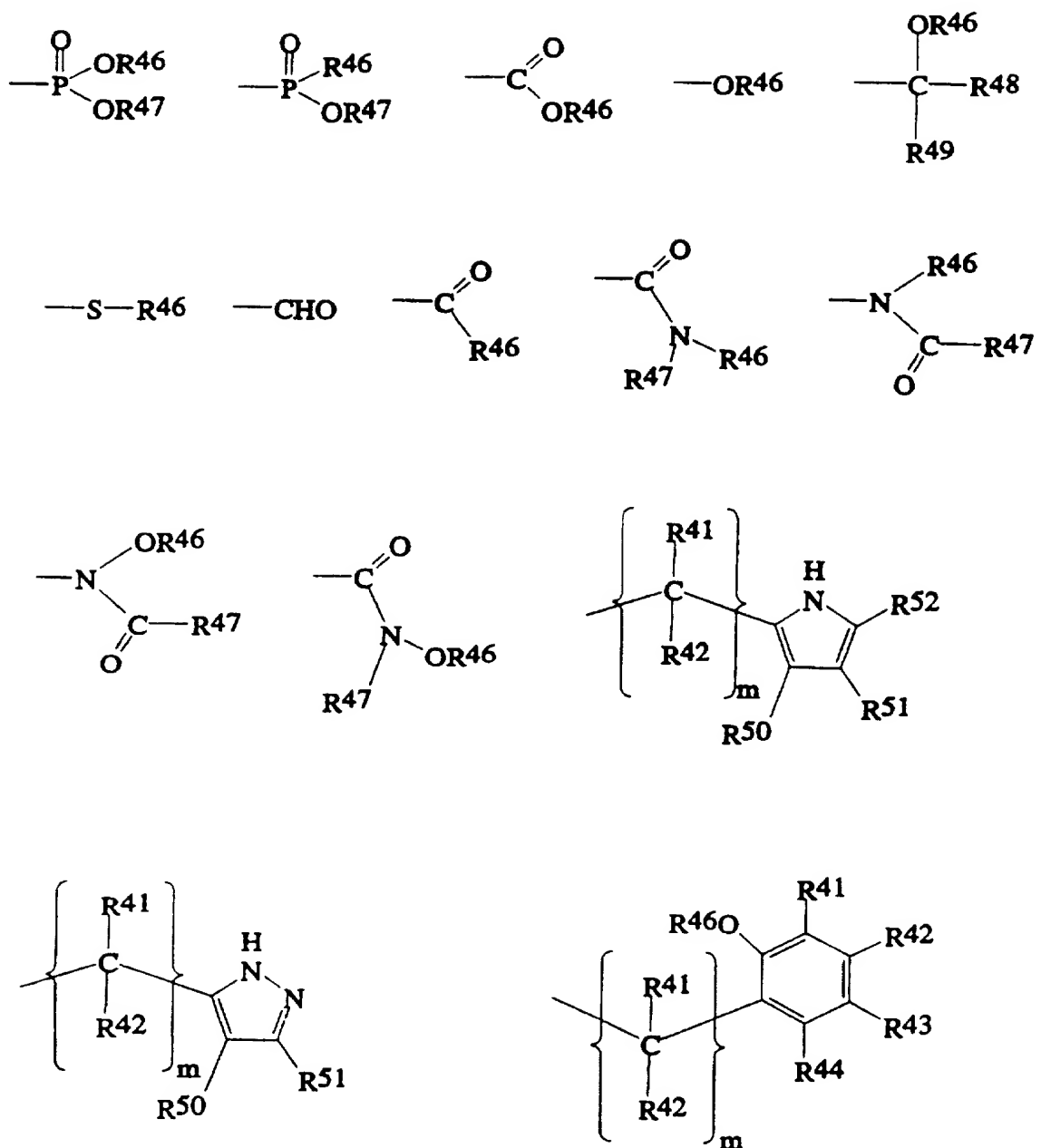
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy,

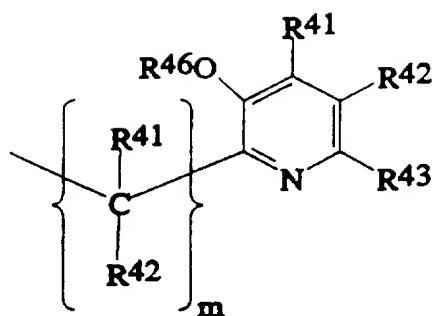
alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

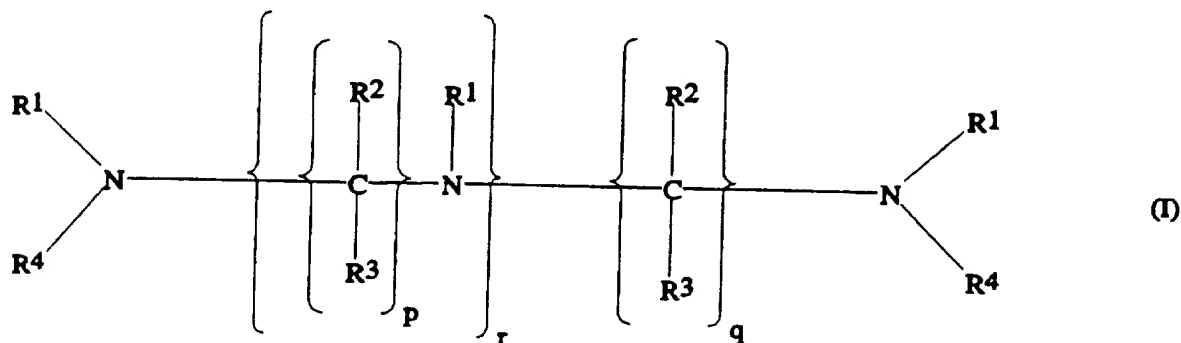
m is an integer of from 1 to 3,

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms; and physiological salts thereof with the proviso that the molecular weight of said complexing agent does not exceed 2000.

2. A method in accordance with claim 1, wherein said surface is a human body surface.

3. A method in accordance with claim 1, wherein said complexing agent is added to a solution.

4. A method for treating conditions dependent on the bioavailability of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:



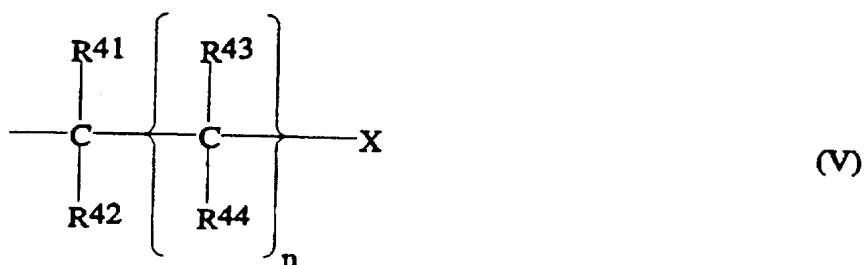
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



wherein,

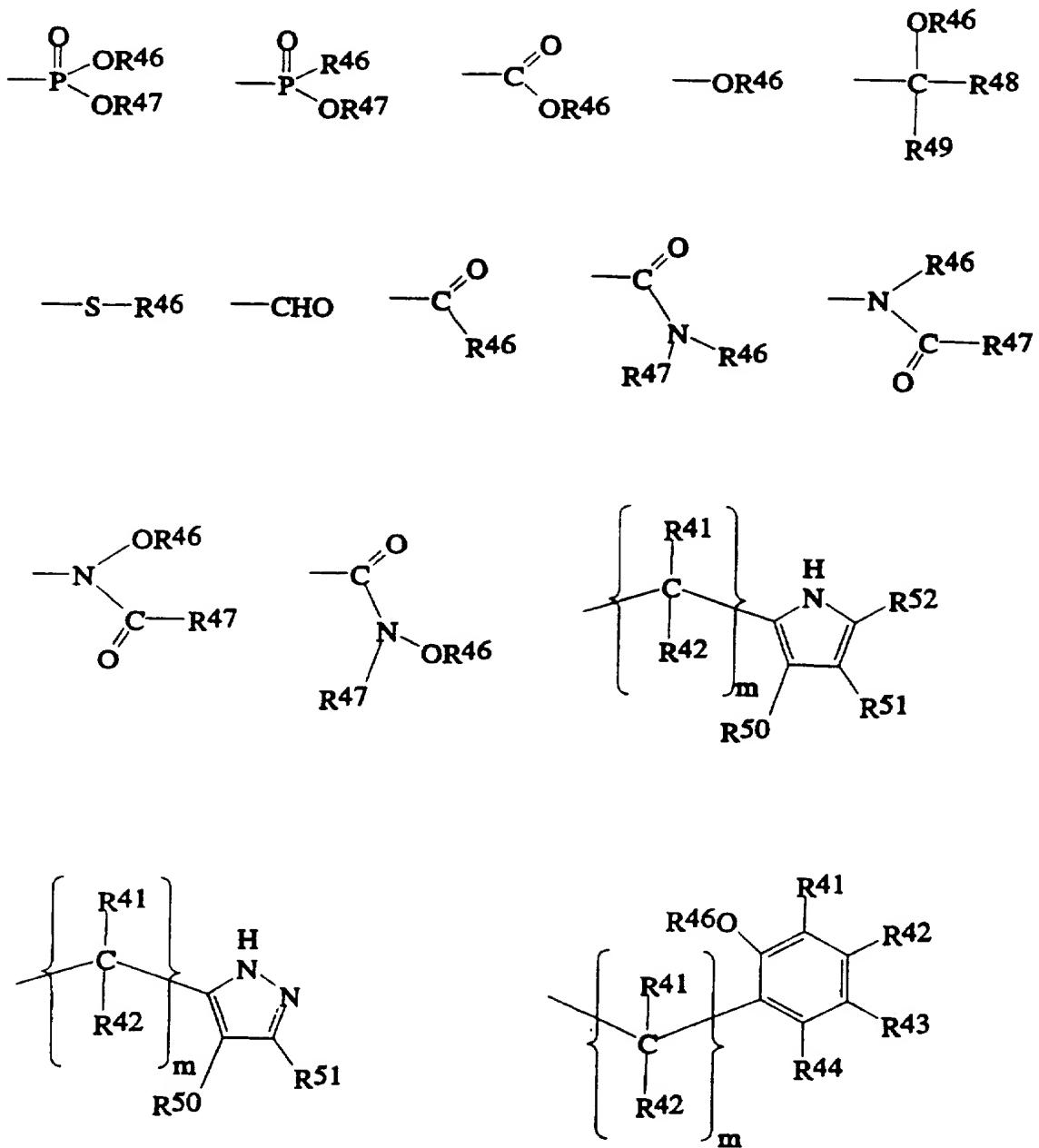
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group

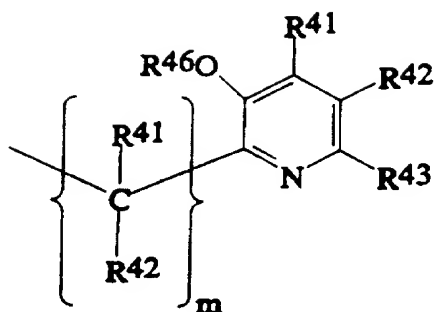
consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

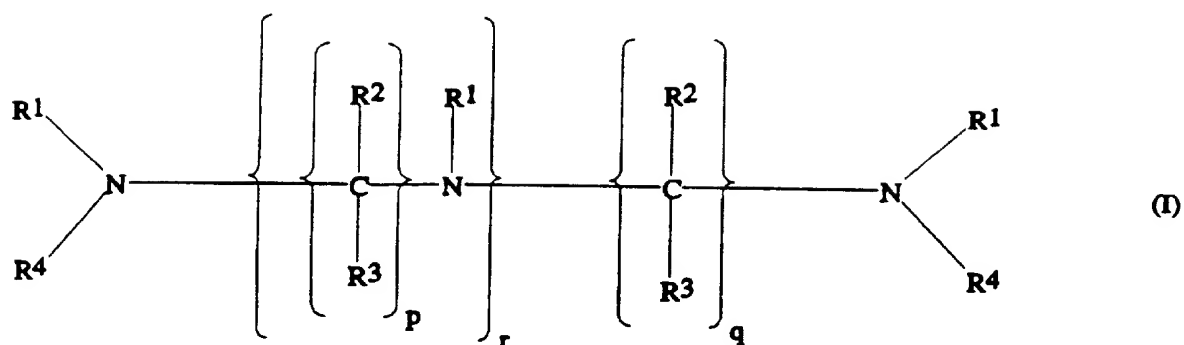
R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and  
m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;  
and physiological salts thereof, with the proviso that the molecular weight of said complexing agent does not exceed 2000; and said complexing agent is present in a pharmaceutically acceptable carrier.

5. A method for treating conditions associated with elevated levels of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:



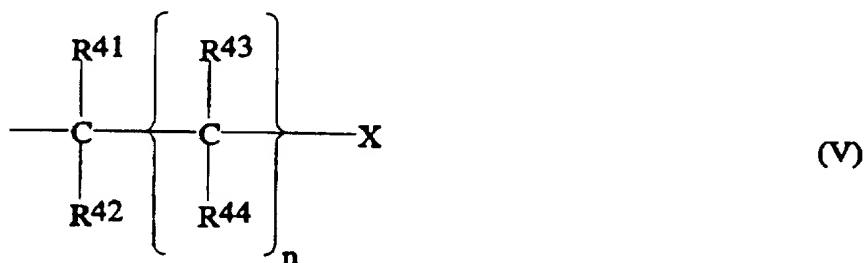
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

$R^2$ ,  $R^3$  and  $R^4$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^1$  is a member selected from the group consisting of  $R^2$ ,  $R^3$ ,  $R^4$ , and radicals of formula:



wherein,

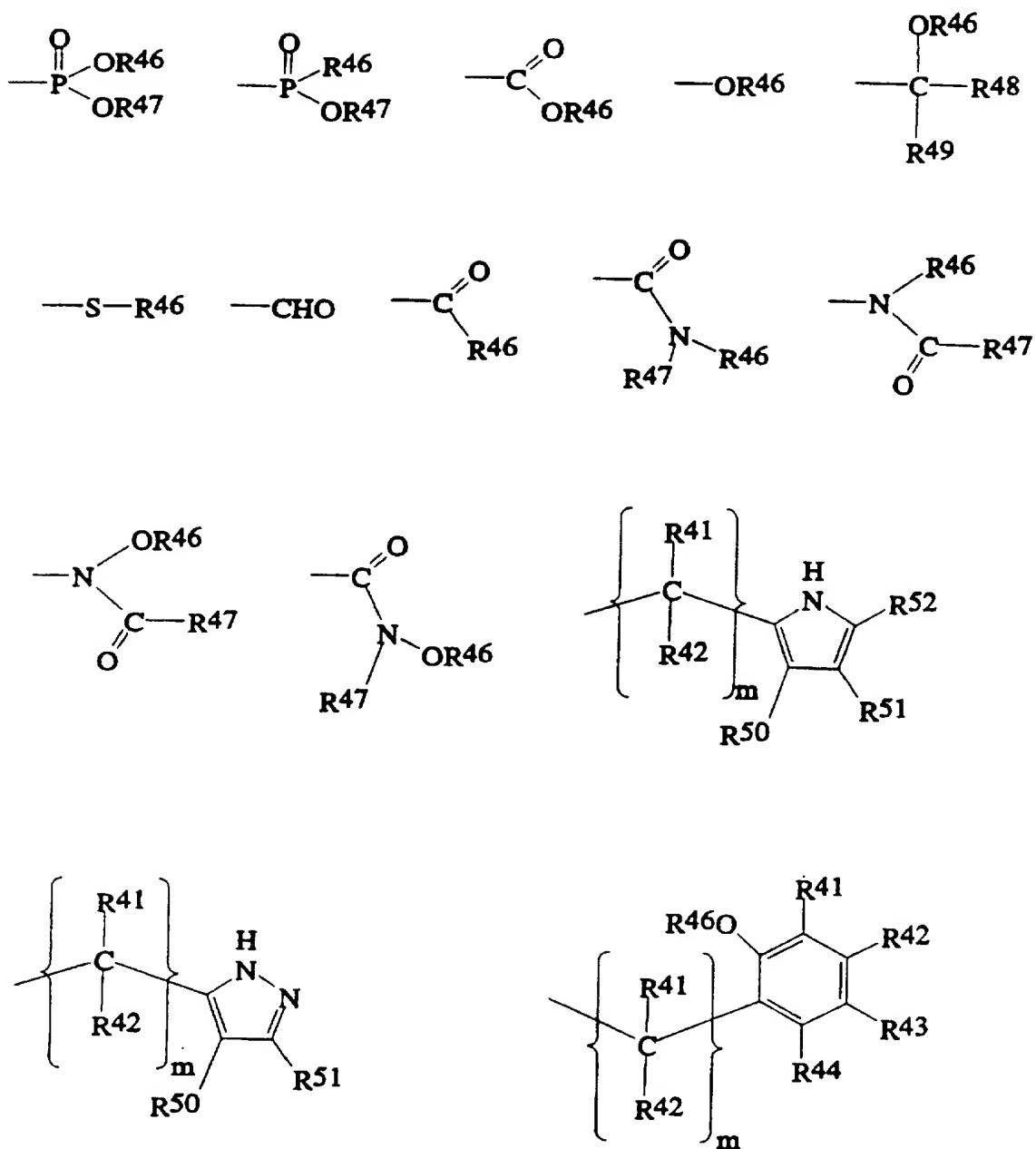
$R^{41}$ ,  $R^{42}$  and  $R^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl

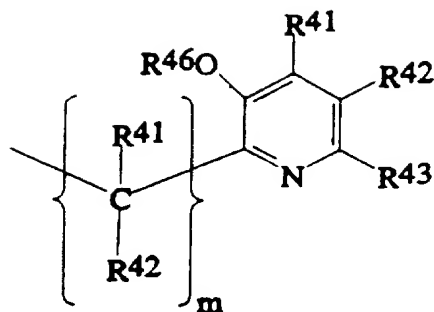
interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

$R^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and  
m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

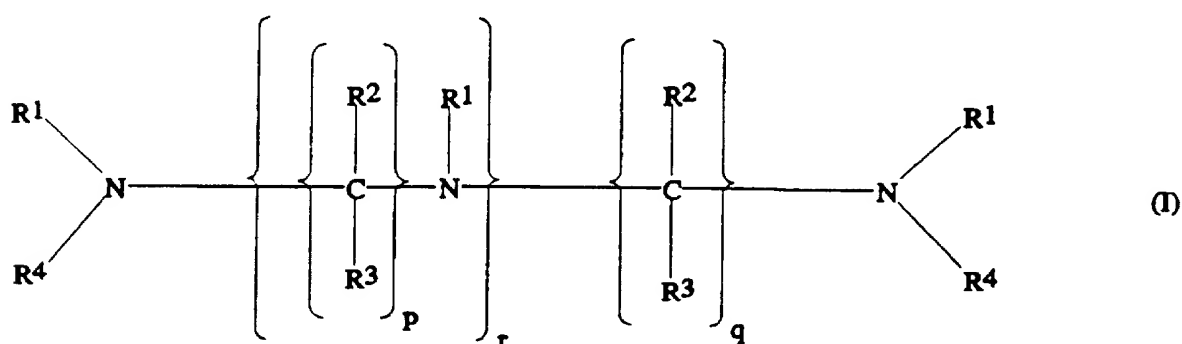
and physiological salts thereof, with the proviso that at least one R<sup>1</sup> group is other than a radical of formula (V) in which X is carboxylic acid and with the further proviso that the molecular weight of said complexing agent does not exceed 2000; and said complexing agent is present in a pharmaceutically acceptable carrier.

6. A method in accordance with claim 4 wherein said conditions are mediated by proliferation of DNA or RNA viruses.

7. A method in accordance with claim 4 wherein said conditions are mediated by cell proliferation.
8. A method in accordance with claim 7 wherein said condition is neoplasia.
9. A method in accordance with claim 7 wherein said condition is a bacterial infection.
10. A method in accordance with claim 7 wherein said condition is a fungal infection.
11. A method in accordance with claim 7 wherein said condition is a protozoal infection.
12. A method in accordance with claim 7 wherein said condition is an inflammatory condition.
13. A method in accordance with claim 7 wherein said condition is an immune disorder.
14. A method in accordance with claim 7 wherein said condition is a pregnancy termination.
15. A method in accordance with claim 7 wherein said condition is a condition further mediated by osteoclast proliferation.
16. A method in accordance with claim 4 wherein said conditions are mediated by free radical or oxidation related tissue destruction.
17. A method in accordance with claim 16 wherein said conditions are selected from the group consisting of rheumatoid arthritis and related disorders.
18. A method in accordance with claim 5, wherein said conditions are selected from the group consisting of hemachromatosis, hemosiderosis and Wilson's disease.

19. A method in accordance with claims 1, 4 or 5, wherein at least two of said  $R^1$  are selected from the group consisting of phosphonic acid-containing radicals, phosphonic acid mono ester-containing radicals, carboxylic acid-containing radicals and combinations thereof.

20. A method for nuclear medical imaging or enhancing contrast in magnetic resonance imaging in a patient, said method comprising;  
administering to said patient a pharmaceutical composition comprising a radioisotopic or paramagnetic first transition series element which is in chelated form with a compound of formula:



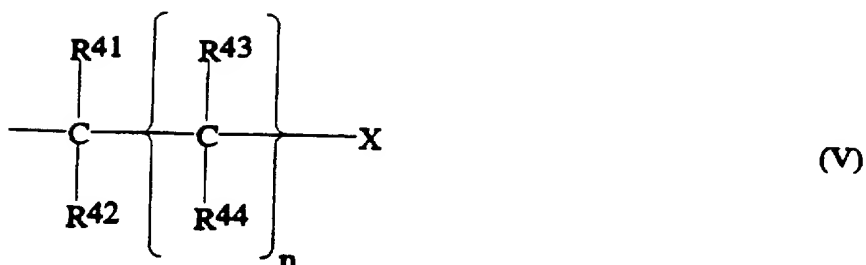
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

$R^2$ ,  $R^3$  and  $R^4$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^1$  is a member selected from the group consisting of  $R^2$ ,  $R^3$ ,  $R^4$ , and radicals of formula:



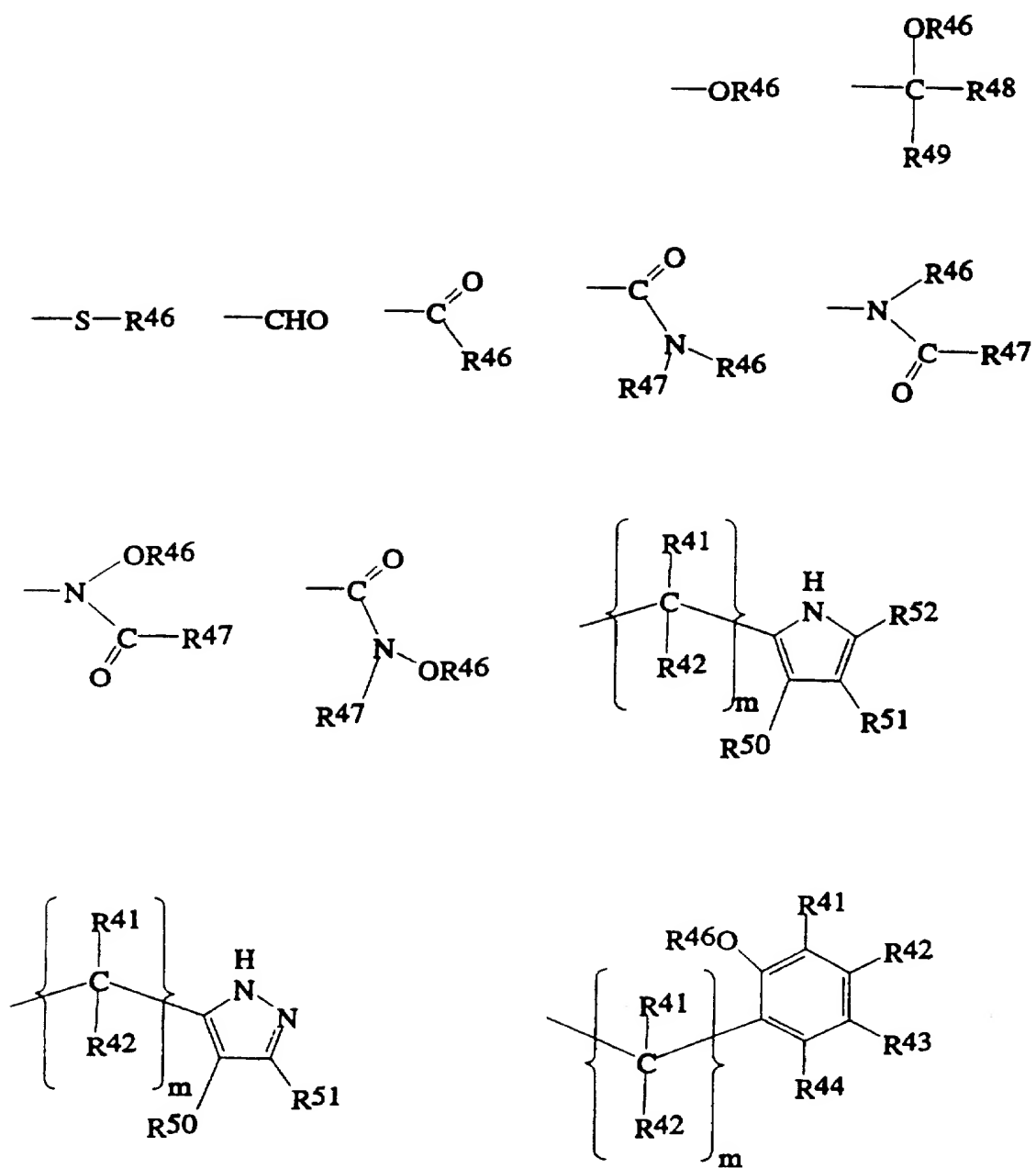
wherein,

**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

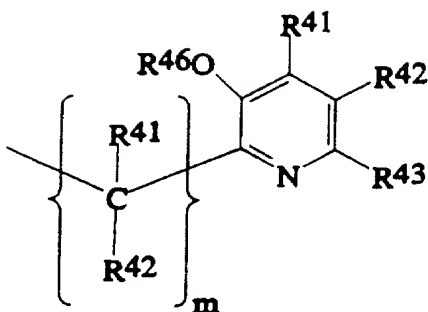
**R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;**

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:



144



wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

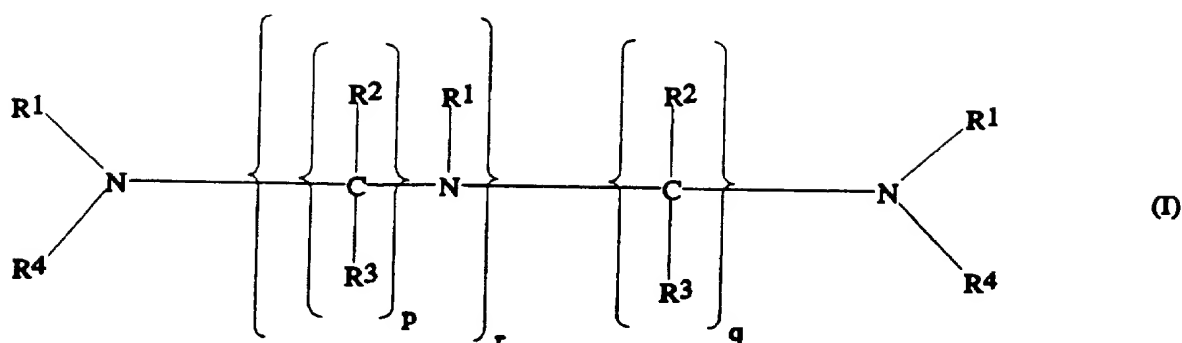
R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms, with the proviso that the molecular weight of said compound does not exceed 2000; and

detecting said radioisotopic or paramagnetic first transition series element.

21. A pharmaceutical composition comprising a compound of the formula:



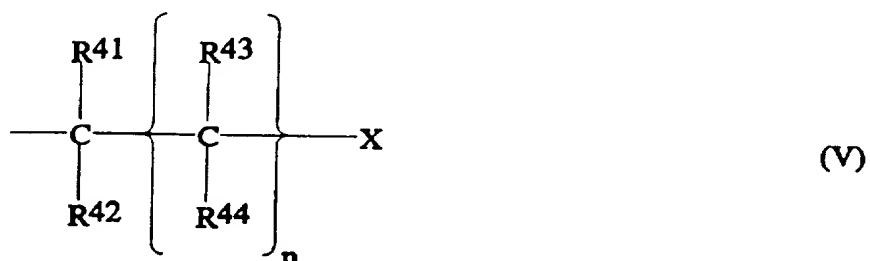
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



wherein,

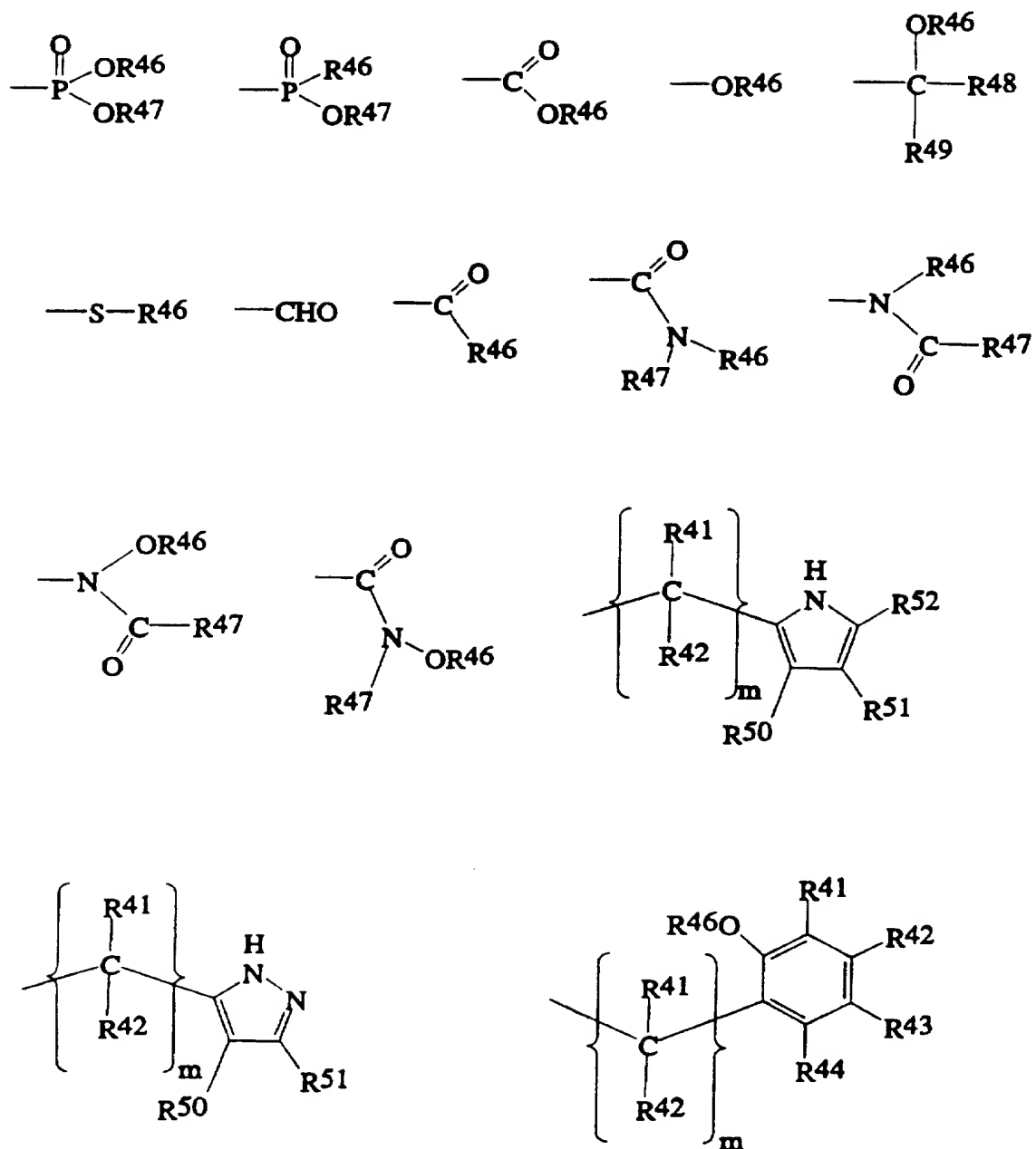
R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl,

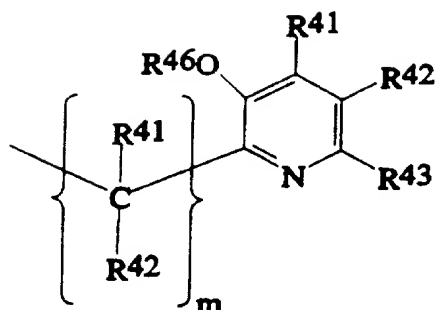
hydroxyarylalkyl, and halogen substituted versions thereof;  
R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:

147





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

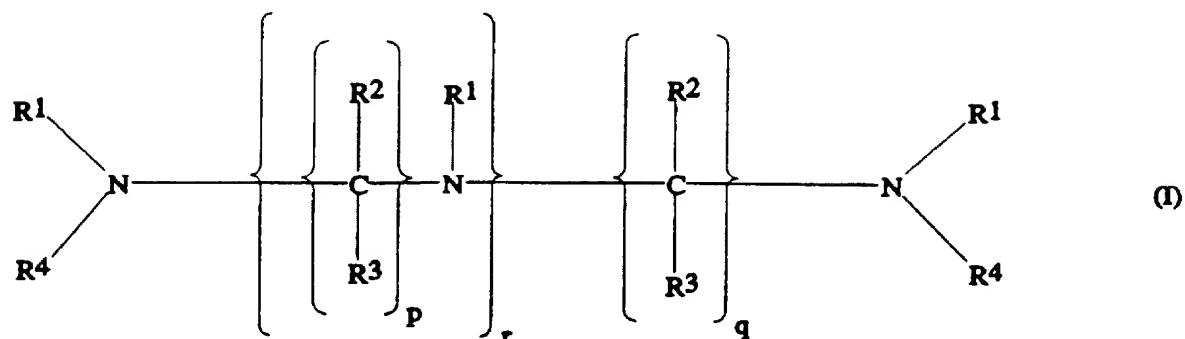
R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and  
m is an integer of from 1 to 3,

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms; and

physiological salts thereof with the proviso that at least one R<sup>1</sup> group is other than a radical of formula (V) in which X is carboxylic acid and with the further proviso that the molecular weight of said compound does not exceed 2000; in a pharmaceutically acceptable carrier.

22. Compounds having the formula:

149



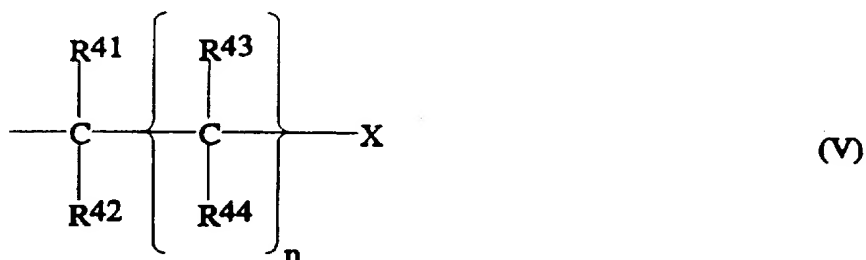
wherein,

p and q are each independently integers of from 2 to 3;

r is an integer of from 0 to 4;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>1</sup> is a member selected from the group consisting of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and radicals of formula:



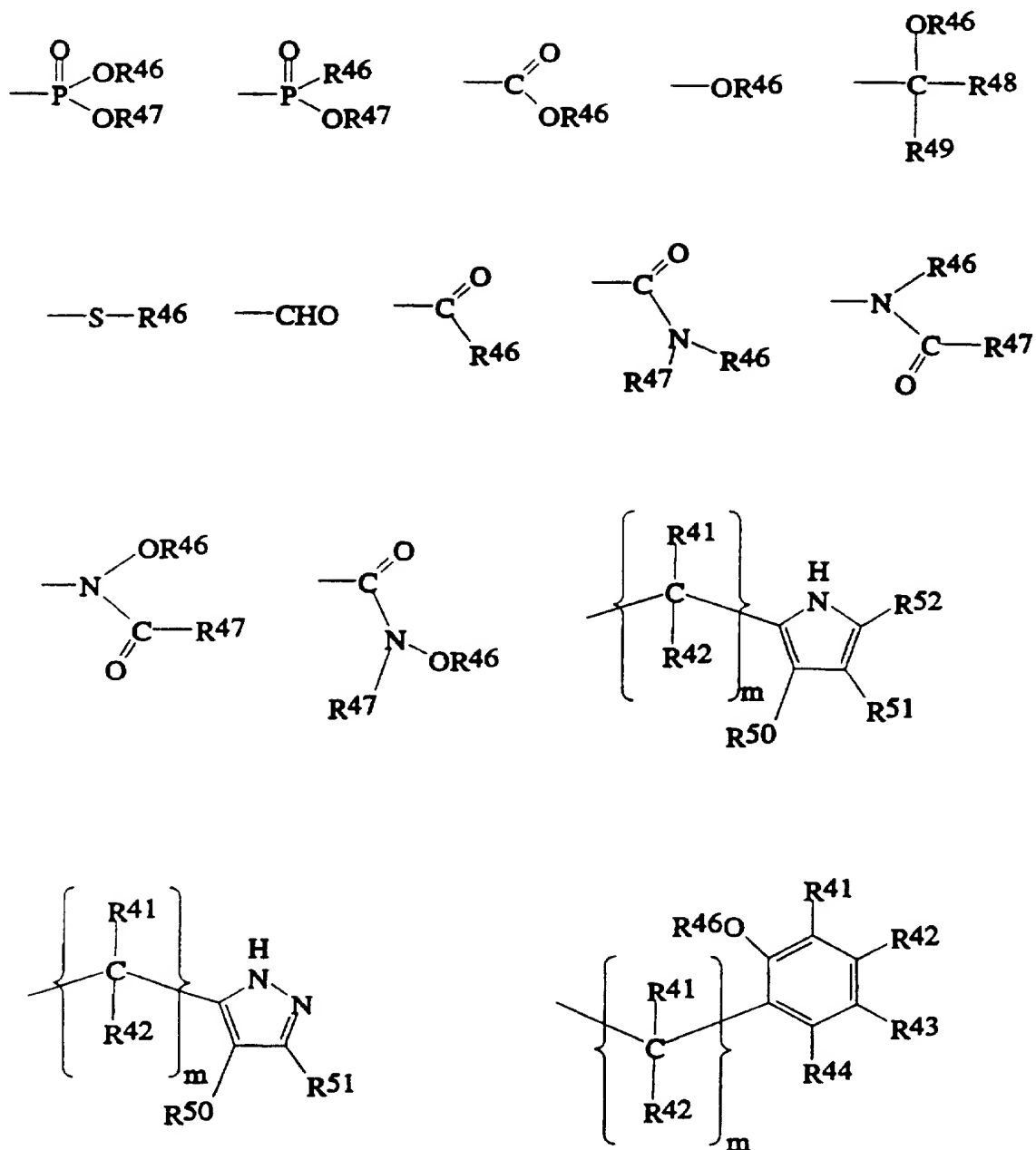
wherein,

R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl,

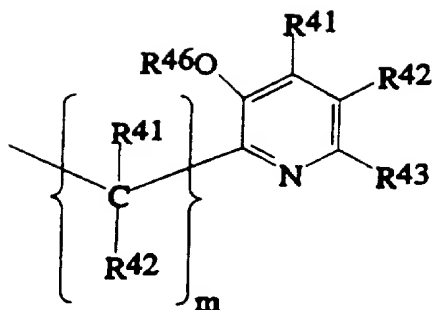
hydroxyarylalkyl, and halogen substituted versions thereof;  
R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

n is zero or 1; and

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:



152



wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl, and aryl, or taken together form a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3,

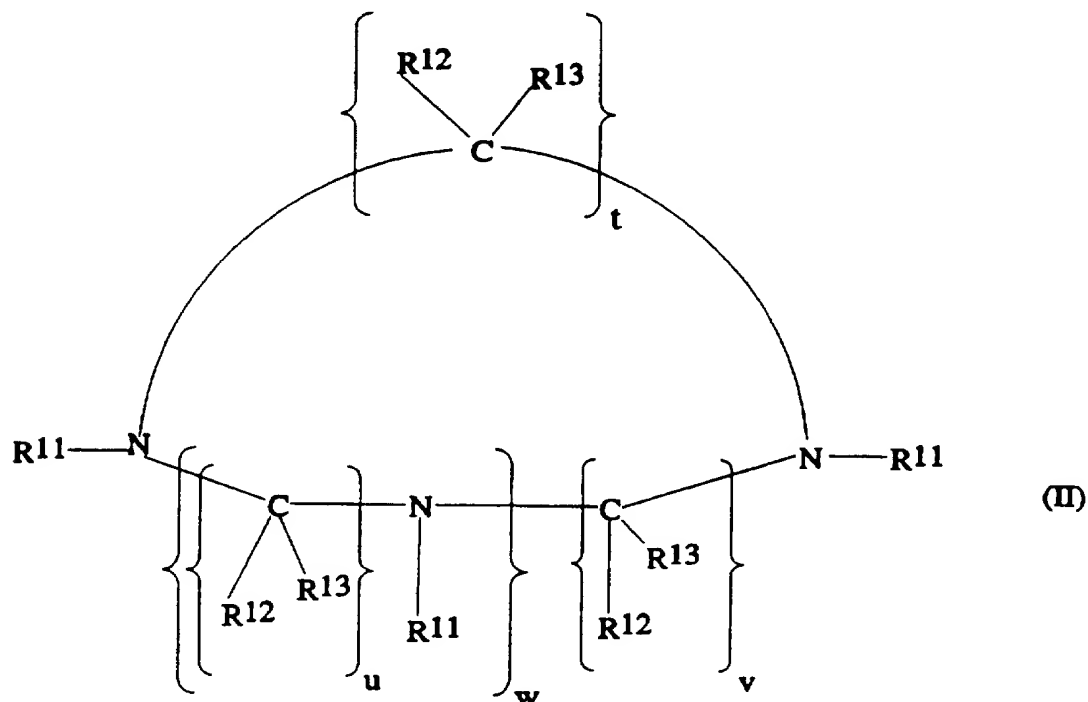
and wherein at least two of said R<sup>1</sup> and R<sup>4</sup> groups comprise at least two contiguous carbon atoms directly attached to nitrogen atoms and the carbon atom in a position  $\beta$  to the nitrogen atom is substituted with a hydroxy and at least one member selected from the group consisting of hydroxymethyl, alkoxymethyl, alkenoxymethyl, aryloxymethyl and combinations thereof;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said compound does not exceed 2000.

23. A compound in accordance with claim 22, wherein the cations of said physiological salts are sodium or N-methyl glucamine.

24. A method for inhibiting bacterial or fungal growth on a surface or in a solution comprising administering to said surface or solution a complexing agent having the formula:



wherein,

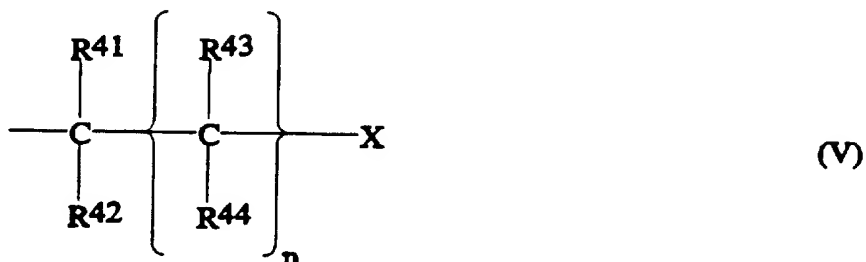
t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted

**versions thereof:**

**R<sup>11</sup> is a member selected from the group consisting of R<sup>12</sup>, R<sup>13</sup> and radicals of formula:**



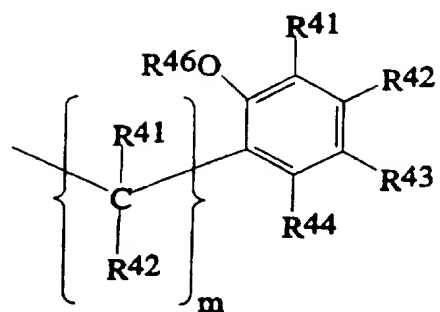
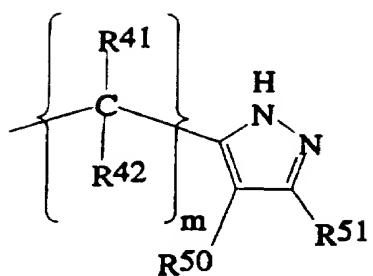
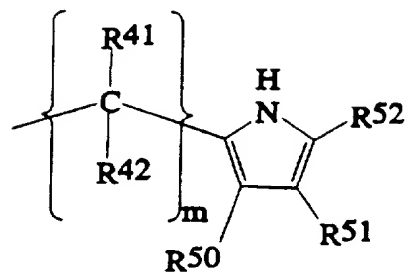
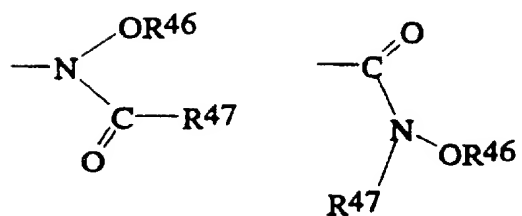
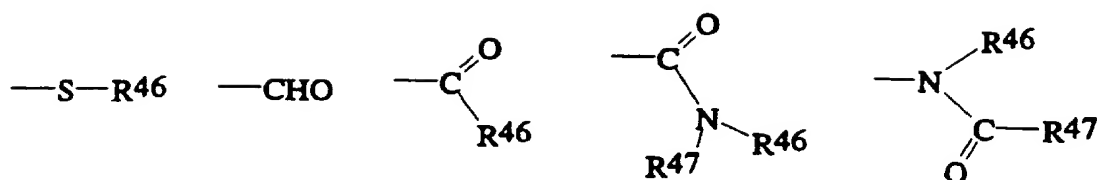
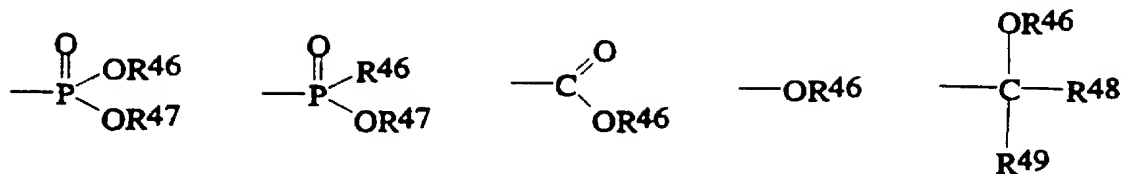
wherein,

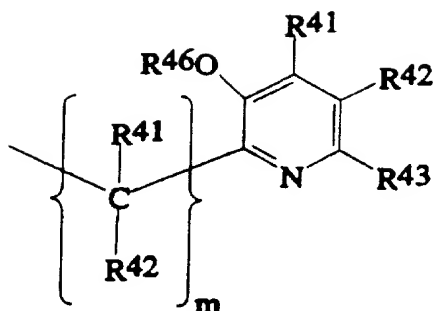
**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

**R<sup>44</sup>** is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3,

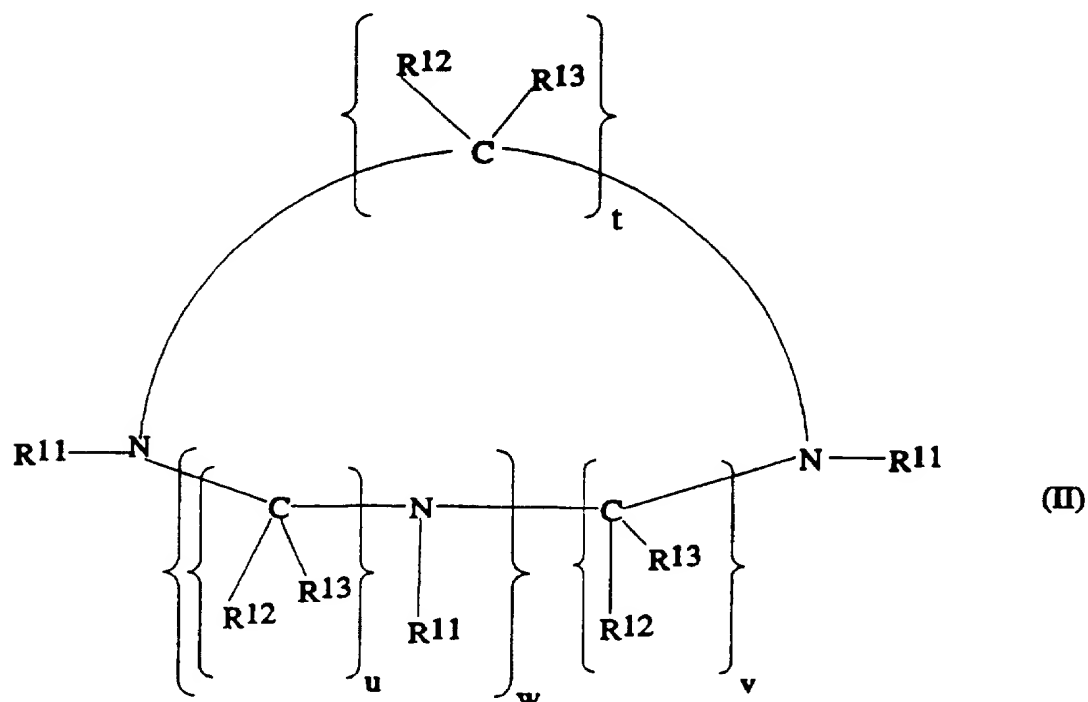
and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said complexing agent does not exceed 2000.

25. A method in accordance with claim 24, wherein said surface is a human body surface.

26. A method in accordance with claim 24, wherein said complexing agent is added to a solution.

27. A method for treating conditions dependent on the bioavailability of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:



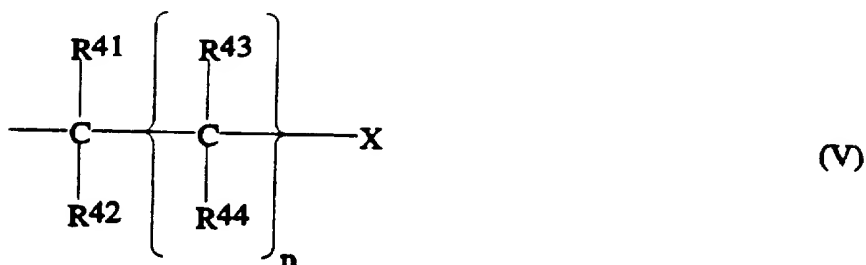
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^{11}$  is a member selected from the group consisting of  $R^{12}$ ,  $R^{13}$  and radicals of formula:



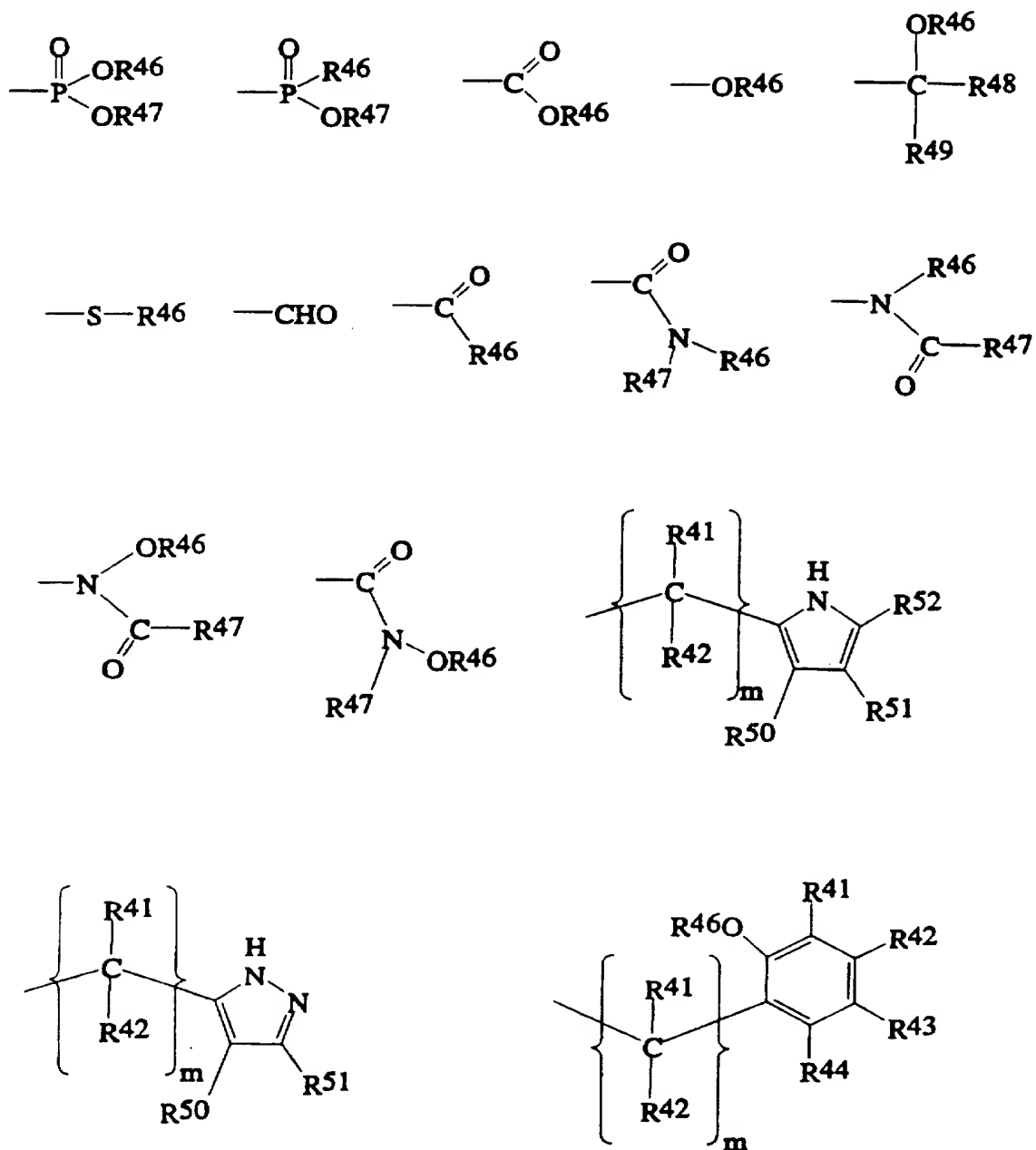
wherein,

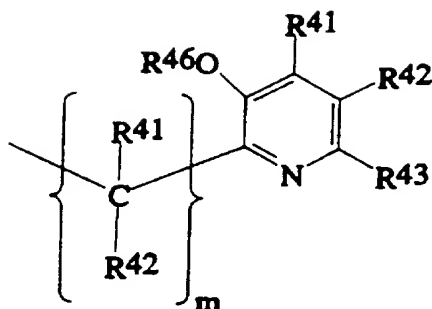
$R^{41}$ ,  $R^{42}$  and  $R^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

$R^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$n$  is zero or 1; and

$X$  is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

$R^{41}$ ,  $R^{42}$ ,  $R^{43}$  and  $R^{44}$  are each independently as described above;

$R^{46}$  and  $R^{47}$  are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

$R^{48}$  and  $R^{49}$  are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$R^{50}$ ,  $R^{51}$  and  $R^{52}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

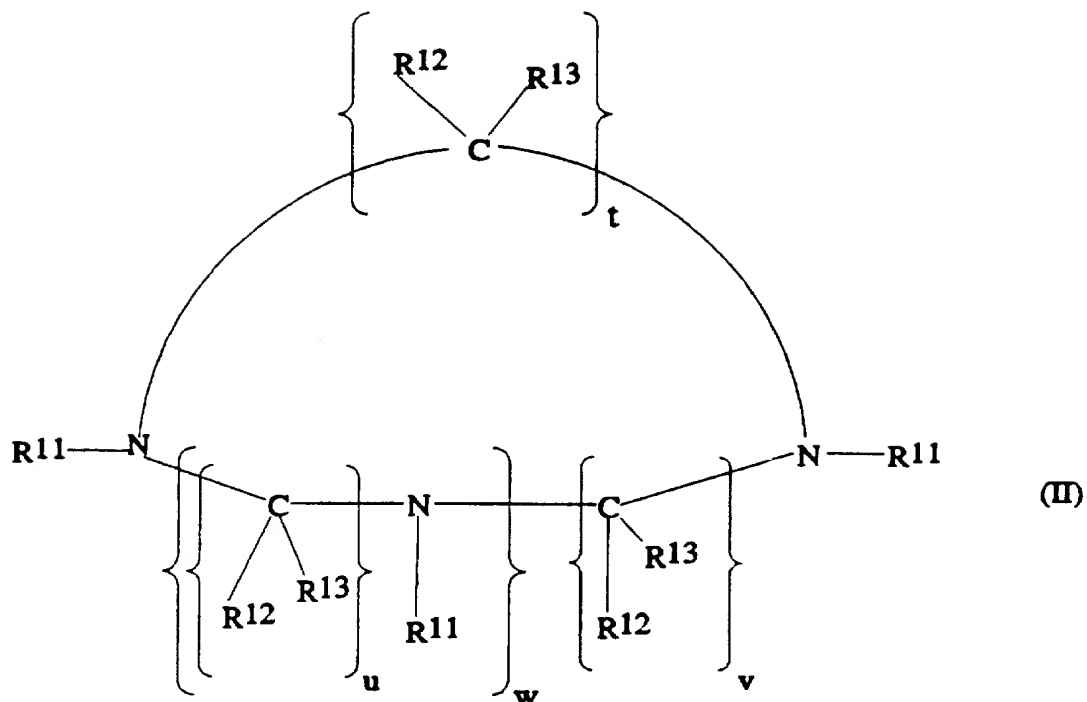
$m$  is an integer of from 1 to 3;

and wherein, optionally, any two of  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

with the proviso that the molecular weight of said complexing agent does not exceed 2000.

28. A method for treating conditions dependent on elevated levels of first transition series elements in a patient, comprising administering to said patient an effective amount of a complexing agent having the formula:

161



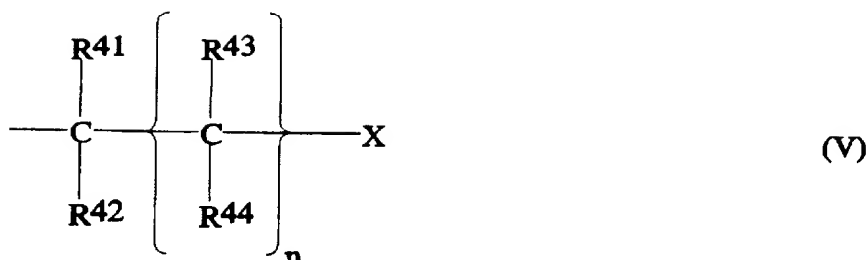
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>11</sup> is a member selected from the group consisting of R<sup>12</sup>, R<sup>13</sup> and radicals of formula:



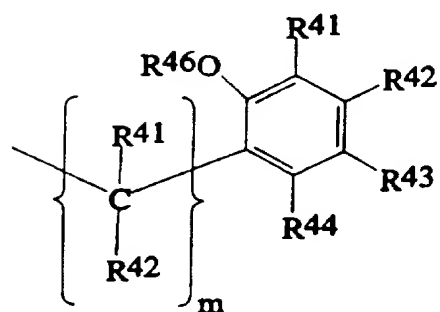
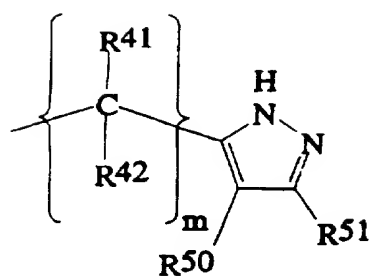
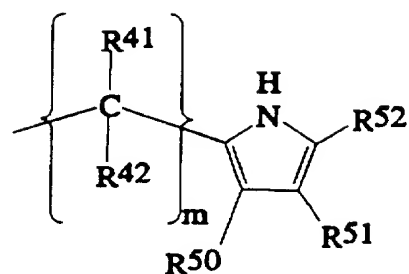
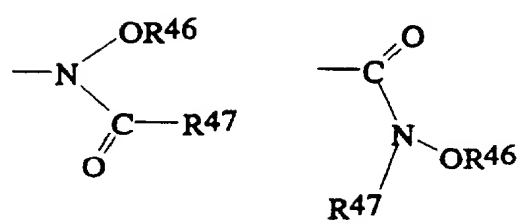
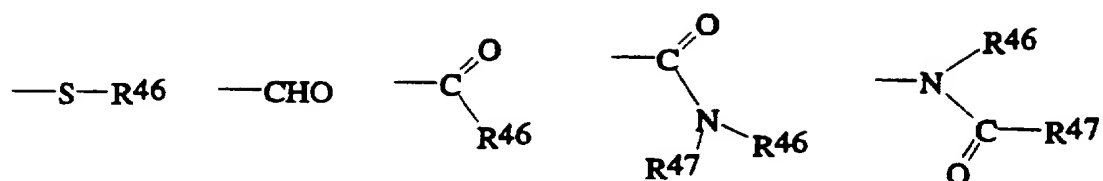
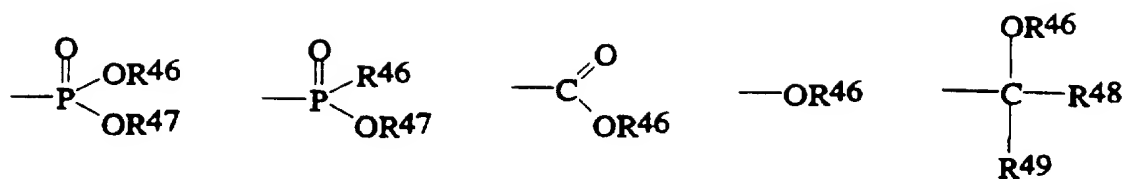
wherein,

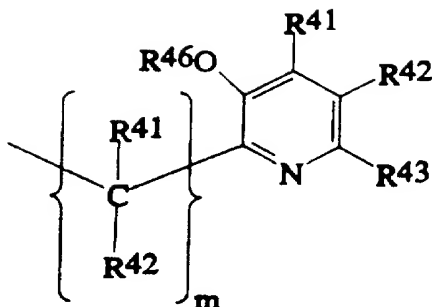
$\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

$\text{R}^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$n$  is zero or 1; and

$X$  is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two complexing agents of formula (I) through a linking group having from 1 to 6 carbon atoms;

with the proviso that the molecular weight of said complexing agent does not exceed 2000.

29. A method in accordance with claim 27 wherein said conditions are mediated by proliferation of DNA or RNA viruses.

**30.** A method in accordance with claim 27 wherein said conditions are mediated by cell proliferation.

**31.** A method in accordance with claim 30, wherein said condition is neoplasia.

**32.** A method in accordance with claim 30, wherein said condition is a bacterial infection.

**33.** A method in accordance with claim 30, wherein said condition is a fungal infection.

**34.** A method in accordance with claim 30, wherein said condition is a protozoal infection.

**35.** A method in accordance with claim 30, wherein said condition is an inflammatory condition.

**36.** A method in accordance with claim 30, wherein said condition is an immune disorder.

**37.** A method in accordance with claim 30, wherein said condition is a pregnancy termination.

**38.** A method in accordance with claim 30, wherein said condition is a condition mediated by osteoclast proliferation.

**39.** A method in accordance with claim 27, wherein said conditions are mediated by free radical or oxidation related tissue destruction.

**40.** A method in accordance with claim 39, wherein said conditions are selected from the group consisting of rheumatoid arthritis and related disorders.

**41.** A method in accordance with claim 28, wherein said conditions are selected from the group consisting of hemachromatosis, hemosiderosis and Wilson's disease.

**42.** A method in accordance with claims 24, 27 or 28, wherein t, u and v are each 2, and w is 1.

**43.** A method in accordance with claim 42 wherein at least two of said R<sup>1</sup> are selected from the group consisting of phosphonic acid-containing radicals, phosphonic acid mono ester-containing radicals, carboxylic acid-containing radicals and combinations thereof.

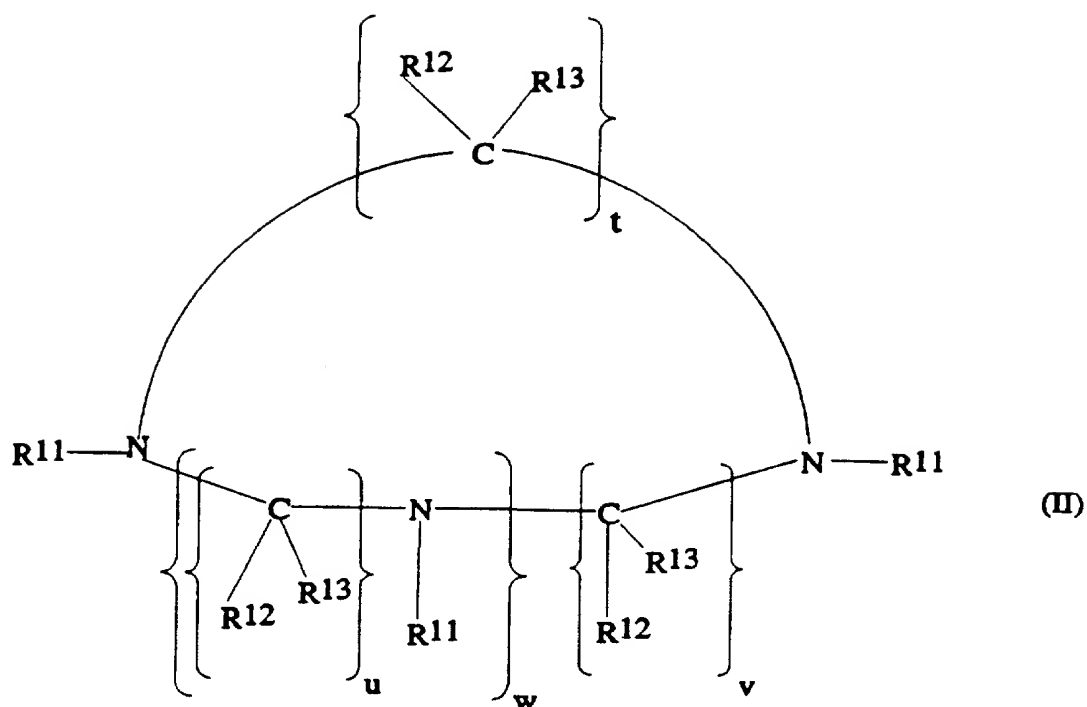
**44.** A method in accordance with claims 24, 27 or 28 wherein t, u and v are each 2, and w is 2.

**45.** A method in accordance with claim 44 wherein at least two of said R<sup>1</sup> are selected from the group consisting of phosphonic acid-containing radicals, phosphonic acid mono ester-containing radicals, carboxylic acid-containing radicals and combinations thereof.

**46.** A method for nuclear medical imaging or enhancing contrast in magnetic resonance imaging in a patient, said method comprising;

administering to said patient a pharmaceutical composition comprising a radioisotopic or paramagnetic first transition series element which is in chelated form with a compound of formula:

167



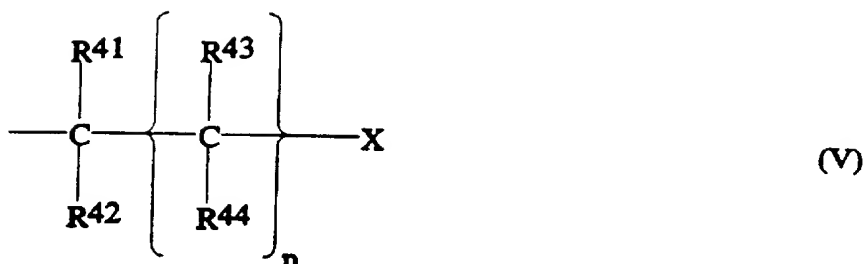
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

$R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^{11}$  is a member selected from the group consisting of  $R^{12}$ ,  $R^{13}$  and radicals of formula:



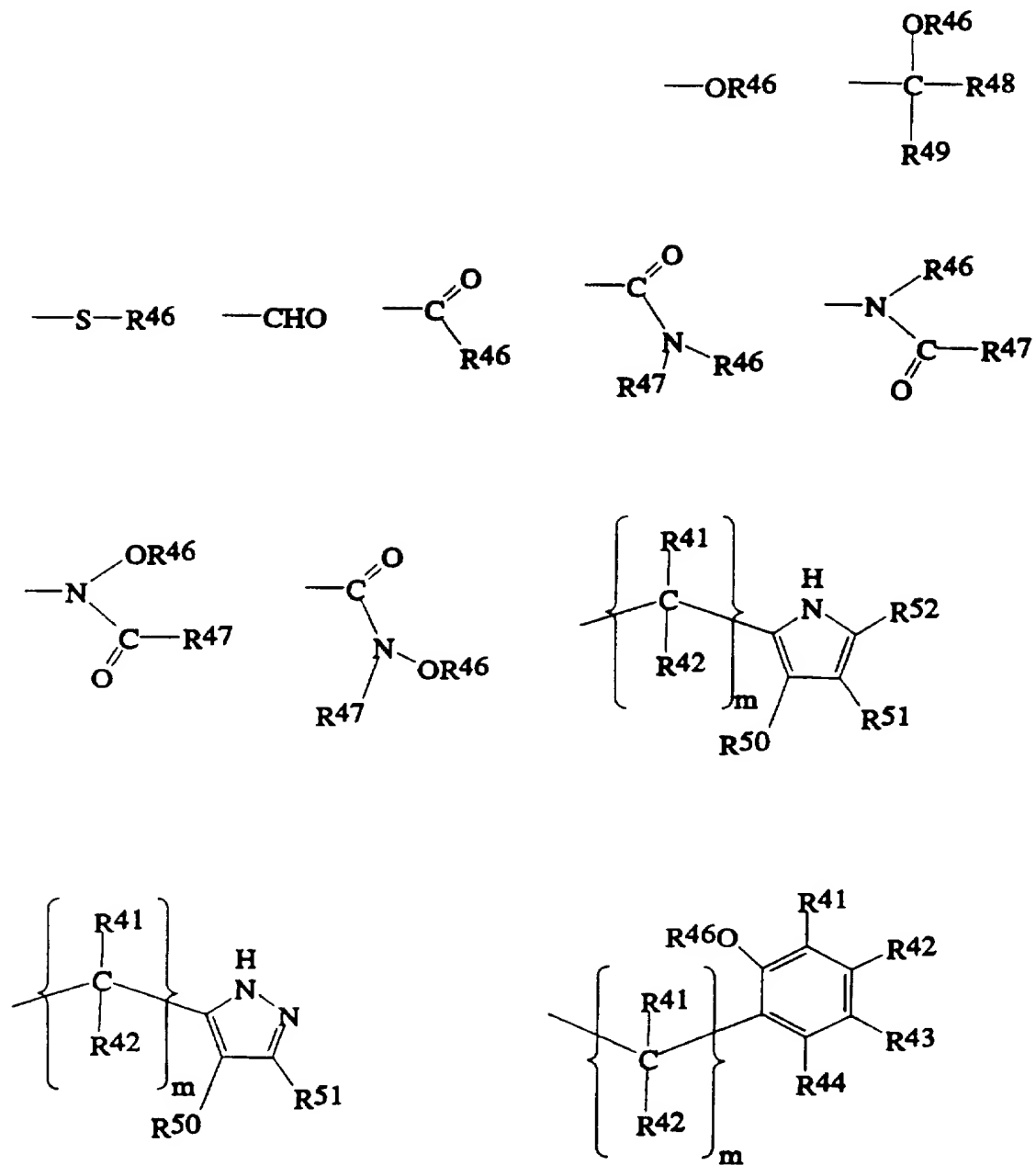
wherein,

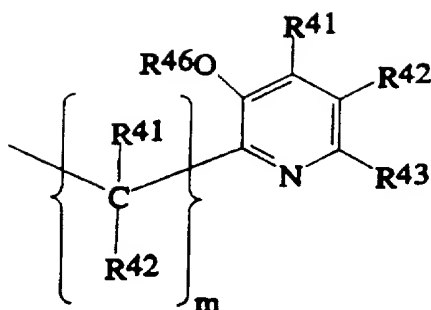
**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

**R<sup>44</sup>** is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein, optionally, any two of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

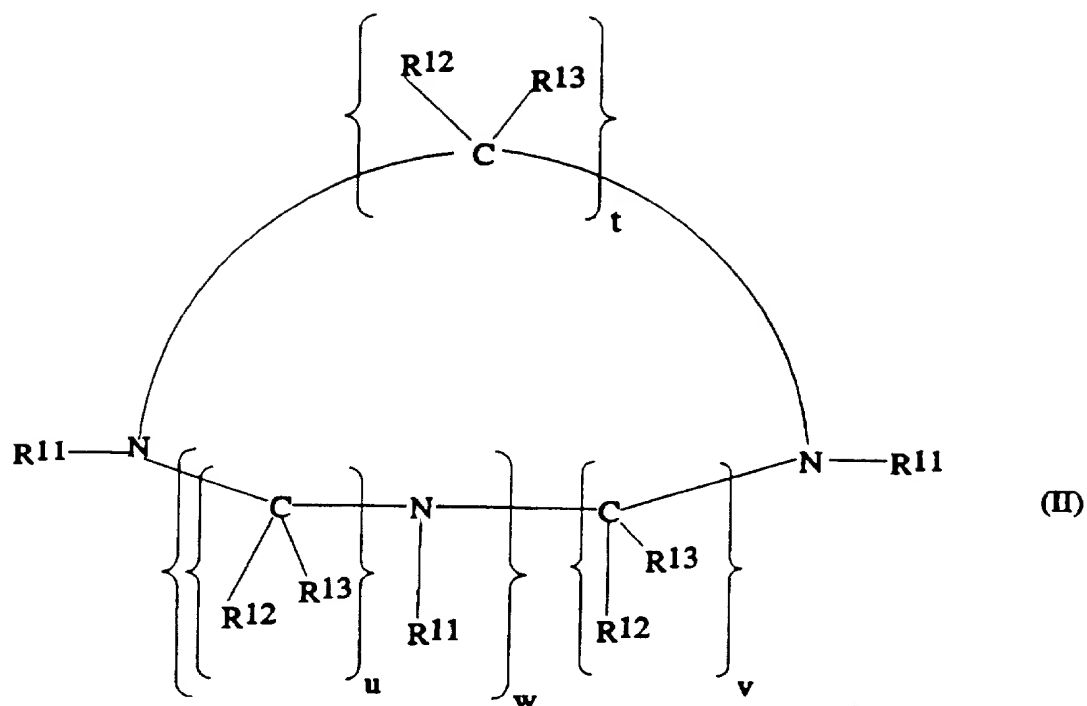
with the proviso that the molecular weight of said compound does not exceed 2000; and

detecting said radioisotopic or paramagnetic first transition series element.

47. A pharmaceutical composition comprising a compound having the

171

formula:



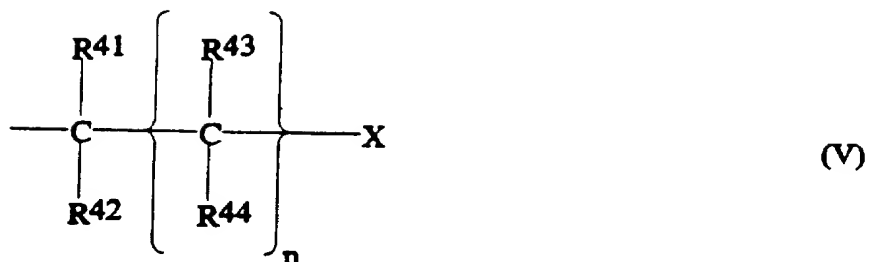
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

$R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

$R^{11}$  is a member selected from the group consisting of  $R^{12}$ ,  $R^{13}$  and radicals of formula:



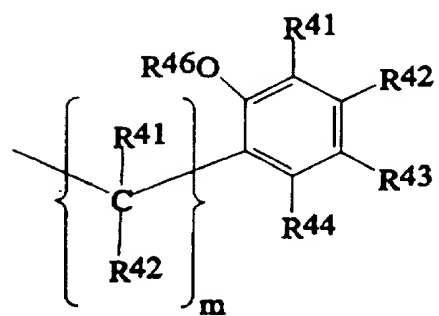
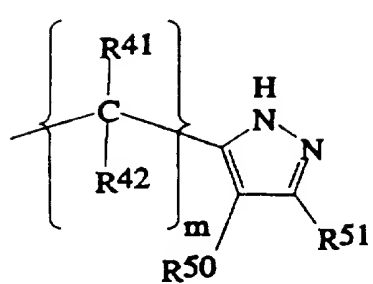
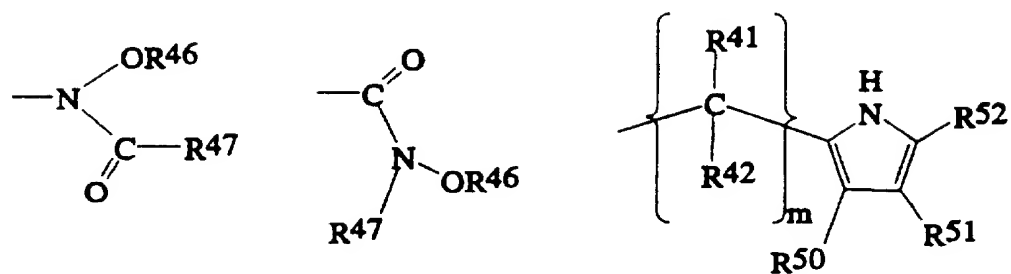
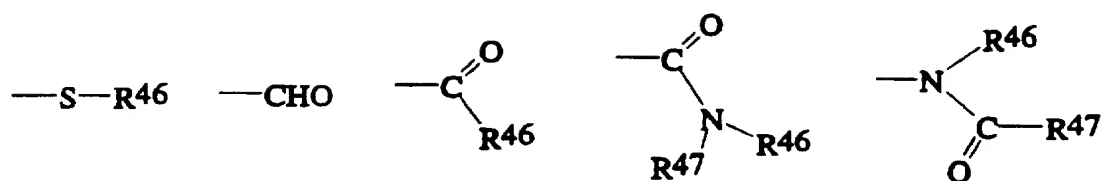
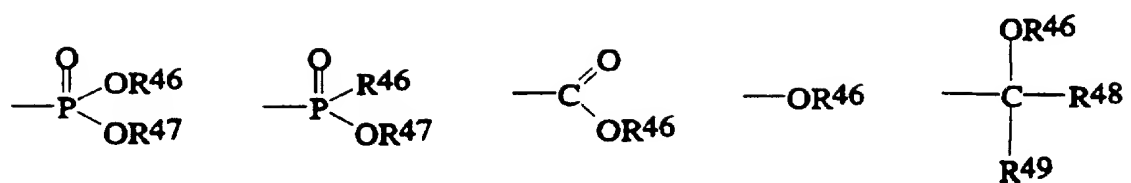
wherein,

**R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;**

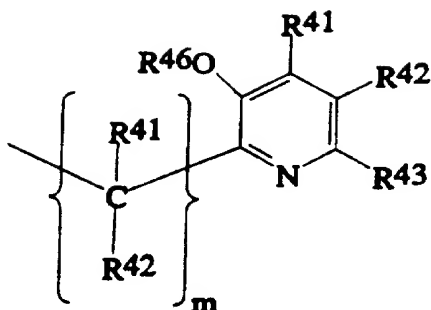
**R<sup>44</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof:**

**n is zero or 1; and**

X is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:



174



wherein

$R^{41}$ ,  $R^{42}$ ,  $R^{43}$  and  $R^{44}$  are each independently as described above;

$R^{46}$  and  $R^{47}$  are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

$R^{48}$  and  $R^{49}$  are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$R^{50}$ ,  $R^{51}$  and  $R^{52}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

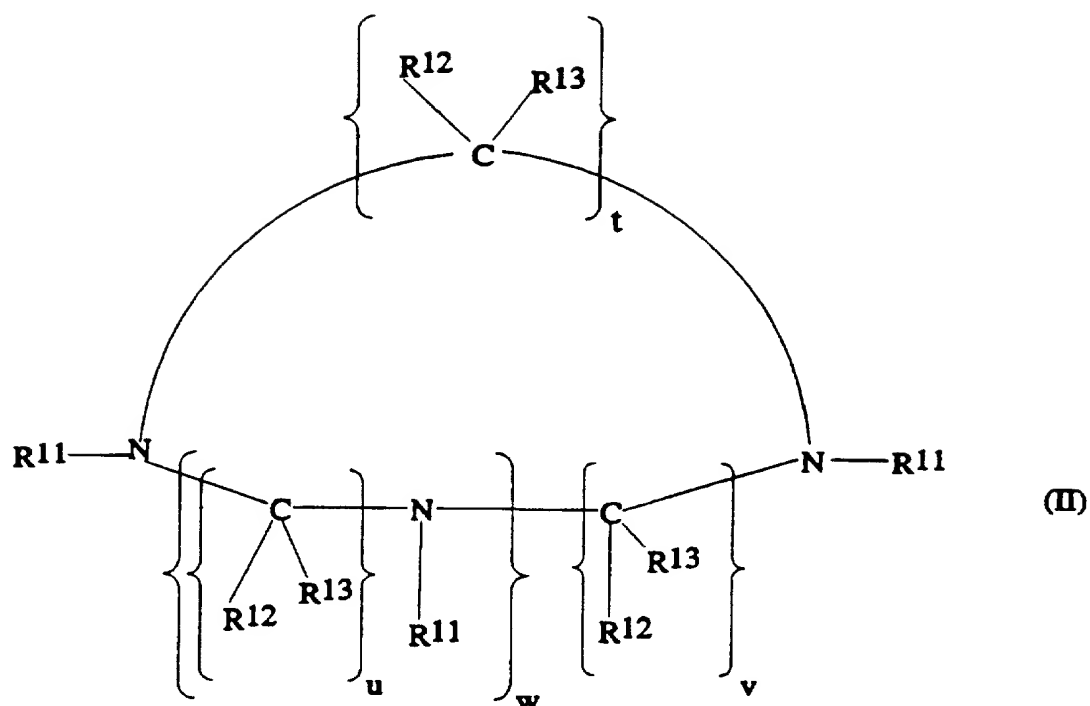
$m$  is an integer of from 1 to 3,

and wherein, optionally, any two of  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of said compound does not exceed 2000; and a pharmaceutically acceptable carrier.

48. Compounds of the formula:

175



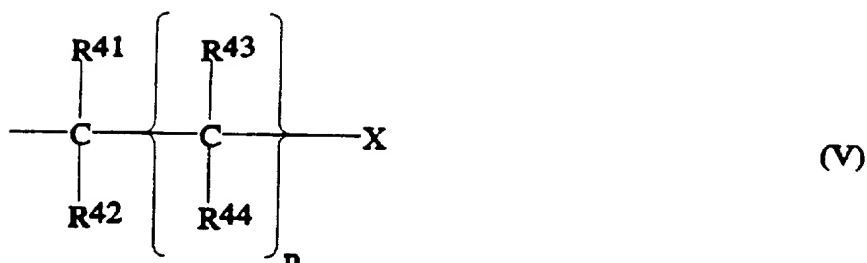
wherein,

t, u and v are each independently 2 or 3;

w is an integer of from 1 to 4;

R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions thereof;

R<sup>11</sup> is a member selected from the group consisting of R<sup>12</sup>, R<sup>13</sup> and radicals of formula:



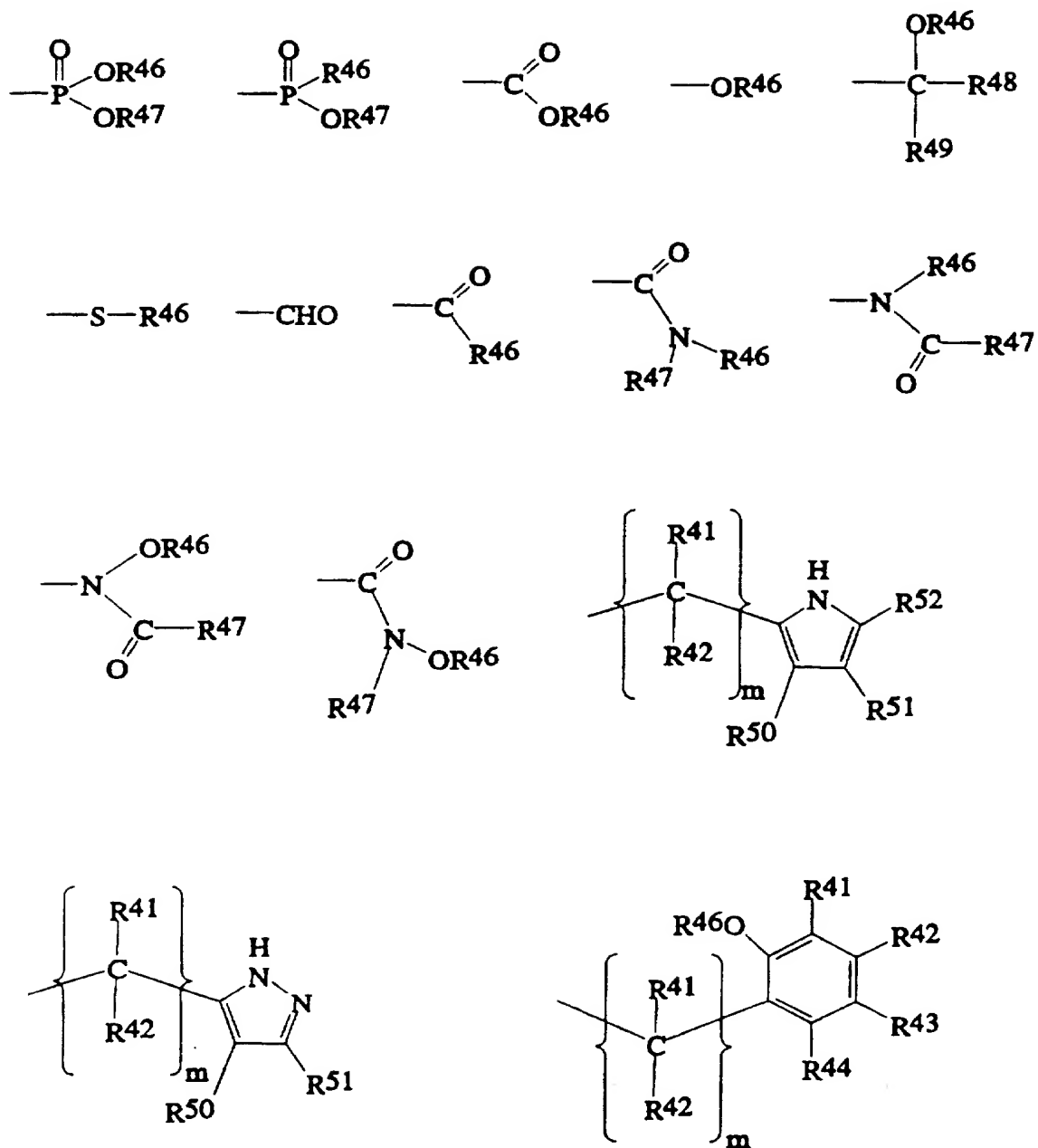
wherein,

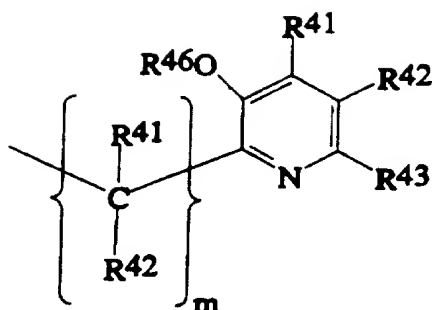
$\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen substituted versions thereof;

$\text{R}^{44}$  is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

$n$  is zero or 1; and

$\text{X}$  is a member selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, aryloxy, arylthio, alkyl interrupted by one or more oxa, alkenyl interrupted by one or more oxa, alkyl interrupted by one or more thia, alkenyl interrupted by one or more thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, halogen substituted versions of each of the above, and radicals selected from the group consisting of:





wherein

R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are each independently as described above;

R<sup>46</sup> and R<sup>47</sup> are each independently selected from the group consisting of H, alkyl and aryl, or taken together form a divalent linking group between the atoms to which they are attached, thereby forming a ring structure;

R<sup>48</sup> and R<sup>49</sup> are each independently selected from the group consisting of H, alkyl, aryl, alkoxy, alkyl interrupted by oxa, aryloxyalkyl, alkoxyaryl, and halogen substituted versions thereof;

R<sup>50</sup>, R<sup>51</sup> and R<sup>52</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkyloxy, alkylthio, alkenyloxy, alkenylthio, aryloxy, arylthio, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl; and

m is an integer of from 1 to 3;

and wherein at least two of said R<sup>11</sup> groups comprise at least two contiguous carbon atoms directly attached to nitrogen atoms and the carbon atom in a position  $\beta$  to the nitrogen atom is substituted with a hydroxy and at least one member selected from the group consisting of hydroxymethyl, alkoxymethyl, alkenoxymethyl, aryloxymethyl and combinations thereof;

and wherein, optionally, any two of R<sup>11</sup>, R<sup>12</sup>, and R<sup>13</sup> are combined to form a ring structure; and dimers thereof, said dimers being formed by the covalent attachment of two compounds of formula (I) through a linking group having from 1 to 6 carbon atoms;

and physiological salts thereof, with the proviso that the molecular weight of

said compound does not exceed 2000.

**49.** A compound in accordance with claim 48, wherein the cation of said physiological salts is sodium or N-methyl glucamine.

# INTERNATIONAL SEARCH REPORT

Intern. Appl. Application No  
PCT/US 96/10785

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K49/00 A61K49/04 A61K51/00 A61K31/13 A61K31/28  
A01N33/02 A01N43/48 A01N43/64 A01N43/713 A61B5/055  
A61B5/05

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 919 177 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 20 February 1963 see the whole document ---	1,3,9,21
X	GB 923 311 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 10 April 1963 see claims 1-10,12 ---	1-3,9,21
X	US 3 398 196 A (MILLER E.J. JR. & MAIS A.) 20 August 1968 see the whole document ---	1,3
X	US 3 432 547 A (GUTTMANN A.T. ET AL.) 11 March 1969 see the whole document ---	1-3,9
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 October 1996

Date of mailing of the international search report

- 4 -02- 1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

HARTRAMPF G.W.

# INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 96/10785

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 13 208 A (TH. GOLDSCHMIDT AG) 28 September 1972 see the whole document ---	1,3
X	GB 1 300 694 A (TH. GOLDSCHMIDT A.G.) 20 December 1972 see the whole document ---	1,3
X	DE 22 62 333 A (TH. GOLDSCHMIDT AG) 11 July 1974 see the whole document ---	1,3
X	US 3 906 105 A (MATT J. & SLOVINSKY M.) 16 September 1975 see the whole document ---	1,3
X	US 3 956 502 A (SLOVINSKY M. & MATT J.) 11 May 1976 see claims 1-3,6-9,12; table I ---	1,3
X	US 4 022 833 A (DIANA G.D. & CUTLER A.R.) 10 May 1977 see examples 35-47, 57 and 58 see column 4, line 38 - line 57; claim 1 ---	1-3,21
X	US 4 072 741 A (HUNSUCKER J.H.) 7 February 1978 see the whole document ---	1,3
X	GB 1 504 390 A (TH. GOLDSCHMIDT A.G.) 22 March 1978 see claims 1-4,12-15 ---	1,3
X	GB 1 513 671 A (L'OREAL) 7 June 1978 see the whole document ---	1-3,9,10
X	EP 0 309 980 A (THE B.F. GOODRICH COMPANY) 5 April 1989 see page 2, line 6; claims 6,7; examples 1-3 ---	1,3
A	FR 2 341 314 A (GOUPIL J.-J.) 16 September 1977  see page 2, line 15 - line 21 see page 3, line 21 - line 38 see page 4, line 27 - line 38 see page 5, line 23 - line 38 see page 6, line 26 - page 7, line 4 see page 8, line 1 - line 15 see page 11, line 32 - line 35 see page 18, line 1 - line 16; claims 1-4 ---	1-5,9, 10,12, 21,22
	-/--	

# INTERNATIONAL SEARCH REPORT

Intern      nal Application No  
PCT/US 96/10785

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 24444 A (BRITISH TECHNOLOGY GROUP LTD.) 9 December 1993 see the whole document ---	1,3
A	EP 0 258 616 A (SALUTAR, INC.) 9 March 1988 see claims 1-3,17-19,28,29 ---	20,46
A	WO 89 01476 A (CELLTECH LIMITED) 23 February 1989 see the whole document ---	20,46
A	FR 2 098 M (SOCIATA ANONYME DES LABORATOIRES ROBERT ET CARRIÈRE) 21 October 1963 see page 1, column 1, paragraph 3 ---	22
A	US 3 271 383 A (YAMAYA W. & MATSUI K.) 6 September 1966 see example 3; table 1 ---	22
A	GB 1 180 210 A (VEB FAHLBERG-LIST CHEMISCHE UND PHARMAZEUTISCHE FABRIKEN) 4 February 1970 see claim 1 ---	21,22
A	DE 22 60 444 A (C.H. BOEHRINGER SOHN) 12 June 1974 see claims 1,4-7; examples 1-6 ---	21,22
A	DE 23 00 543 A (BASF AG) 11 July 1974 see examples 29-32, 56, 57, 82-84, 109 and 110 see claims 1-10 ---	21,22
A	CH 599 924 A (C.H. BOEHRINGER SOHN) 15 June 1978 see the whole document -----	22

# INTERNATIONAL SEARCH REPORT

1 national application No.

PCT/US 96/ 10785

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- |                          |                                 |
|--------------------------|---------------------------------|
| 1. Claims 1-3 (part.)    | 2. Claims 1-3 (part.) and 24-26 |
| 3. Claims 4-19 and 27-45 | 4. Claims 20 and 46             |
| 5. Claim 21              | 6. Claims 22, 23, 48 and 49     |

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-919177		NONE	
GB-A-923311		NONE	
US-A-3398196	20-08-68	DE-A- 1493443 FR-A- 1462117 GB-A- 1135048 GB-A- 1135050 SE-B- 333739	06-11-69 22-02-67  29-03-71
US-A-3432547	11-03-69	NONE	
DE-A-2113208	28-09-72	NONE	
GB-A-1300694	20-12-72	AT-A- 303269 BE-A- 761318 CH-A- 534480 DE-A- 2009276 FR-A- 2080797 NL-A,B 7100500 SE-B- 362585 US-A- 3912816	15-10-72 16-06-71 15-03-73 13-05-71 19-11-71 31-08-71 17-12-73 14-10-75
DE-A-2262333	11-07-74	AT-B- 327401 BE-A- 806413 CH-A- 592046 FR-A- 2211449 NL-A- 7317529	26-01-76 15-02-74 14-10-77 19-07-74 24-06-74
US-A-3906105	16-09-75	CA-A- 1042017	07-11-78
US-A-3956502	11-05-76	NONE	
US-A-4022833	10-05-77	US-A- 3928427 US-A- 4085144 US-A- 4119668 US-A- 4140860	23-12-75 18-04-78 10-10-78 20-02-79
US-A-4072741	07-02-78	NONE	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1504390	22-03-78	DE-A- 2457257	10-06-76
		BE-A- 836285	01-04-76
		FR-A- 2293418	02-07-76
		NL-A- 7513889	09-06-76
-----			
GB-A-1513671	07-06-78	LU-A- 70095	13-04-76
		LU-A- 71848	05-01-77
		BE-A- 829082	14-11-75
		BE-A- 829083	14-11-75
		CA-A- 1074497	25-03-80
		CA-A- 1134865	02-11-82
		CH-A- 611635	15-06-79
		CH-A- 629177	15-04-82
		DE-A- 2521898	04-12-75
		DE-A- 2521899	04-12-75
		FR-A- 2333012	24-06-77
		FR-A- 2270851	12-12-75
		GB-A- 1508215	19-04-78
		NL-A- 7505669	18-11-75
		NL-A- 7505672	18-11-75
-----			
EP-A-309980	05-04-89	JP-A- 1163160	27-06-89
		US-A- 5189173	23-02-93
-----			
FR-A-2341314	16-09-77	BE-A- 850982	31-05-77
		CA-A- 1109471	22-09-81
		CH-A- 622514	15-04-81
		DE-A- 2706826	01-09-77
		GB-A- 1578471	05-11-80
		US-A- 4323550	06-04-82
-----			
WO-A-9324444	09-12-93	EP-A- 0650471	03-05-95
		GB-A,B 2267438	08-12-93
		JP-T- 7507294	10-08-95
		US-A- 5464873	07-11-95
		US-A- 5583261	10-12-96
-----			
EP-A-258616	09-03-88	US-A- 5039512	13-08-91
		AT-T- 138809	15-06-96
		AU-B- 608759	18-04-91

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-258616		AU-A- 7573587	11-02-88
		CA-A- 1321346	17-08-93
		DE-D- 3751829	11-07-96
		DE-T- 3751829	31-10-96
		DE-A- 3777727	30-04-92
		EP-A- 0463644	02-01-92
		ES-T- 2087938	01-08-96
		FI-C- 88677	28-06-93
		IE-B- 64108	12-07-95
		NO-C- 173767	02-02-94
		US-A- 5219553	15-06-93
		JP-A- 63119446	24-05-88
-----			
WO-A-8901476	23-02-89	AT-T- 136302	15-04-96
		AU-B- 629515	08-10-92
		AU-A- 2253388	09-03-89
		DE-D- 3855177	09-05-96
		DE-T- 3855177	02-10-96
		EP-A- 0328589	23-08-89
		JP-T- 2501141	19-04-90
-----			
FR-M-2098		NONE	
-----			
US-A-3271383	06-09-66	NONE	
-----			
GB-A-1180210	04-02-70	BE-A- 730691	01-09-69
		CH-A- 513110	30-09-71
		DE-A- 1901549	20-08-70
-----			
DE-A-2260444	12-06-74	AT-B- 323131	25-06-75
		AT-B- 323132	25-06-75
		AT-B- 325022	25-09-75
		AT-B- 325023	25-09-75
		AT-B- 326107	25-11-75
		AU-A- 5294473	12-09-74
		CH-A- 601182	30-06-78
		CH-A- 599924	15-06-78
		CH-A- 605630	13-10-78
		CH-A- 605633	13-10-78
		CH-A- 605634	13-10-78

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2260444		CH-A- 605631	13-10-78
		CH-A- 605632	13-10-78
		FR-A- 2175055	19-10-73
		GB-A- 1431341	07-04-76
		JP-C- 1194741	12-03-84
		JP-A- 48103532	25-12-73
		JP-B- 58025657	28-05-83
		NL-A- 7303097	10-09-73
		SE-B- 413402	27-05-80
		US-A- 3888898	10-06-75
		US-A- 3969512	13-07-76
		US-A- 3975539	17-08-76
DE-A-2300543	11-07-74	NONE	
CH-A-599924	15-06-78	DE-A- 2210620	20-09-73
		DE-A- 2260444	12-06-74
		AT-B- 323131	25-06-75
		AT-B- 323132	25-06-75
		AT-B- 325022	25-09-75
		AT-B- 323133	25-06-75
		AT-B- 325023	25-09-75
		AT-B- 323134	25-06-75
		AT-B- 326107	25-11-75
		AU-A- 5294473	12-09-74
		BE-A- 796356	06-09-73
		CH-A- 601182	30-06-78
		CH-A- 605630	13-10-78
		CH-A- 605633	13-10-78
		CH-A- 605634	13-10-78
		CH-A- 605631	13-10-78
		CH-A- 605632	13-10-78
		FR-A- 2175055	19-10-73
		GB-A- 1431341	07-04-76
		JP-C- 1194741	12-03-84
		JP-A- 48103532	25-12-73
		JP-B- 58025657	28-05-83
		NL-A- 7303097	10-09-73
		SE-B- 413402	27-05-80
		US-A- 3888898	10-06-75

## INTERNATIONAL SEARCH REPORT

### Information on patent family members

Inter.	nal Application No
--------	--------------------

PCT/US 96/10785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A-599924		US-A- 3969512	13-07-76
		US-A- 3975539	17-08-76
-----			